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Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCAN-CC) – Automated Text Messages, Phone Calls and Face-to-face Interviews: Protocol of a population based randomized controlled trial

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TITLE PAGE

Title: Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCAN-CC) – Automated Text Messages, Phone Calls and Face-to-face Interviews: Protocol of a population based randomized controlled trial

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ABSTRACT

Introduction

Screening is highly effective for cervical cancer prevention and control. Population based screening programs are widely implemented in high income countries, though adherence is often low. The most effective adherence raising strategies are based on patient reminders, small/mass media and face-to-face educational programs, but sequential interventions targeting the general population have seldom been evaluated.

The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organized cervical cancer screening: step 1a – customized text message invitation; step 1b – customized automated phone call invitation; step 2 – secretary phone call; step 3 – family health professional phone call and face-to-face appointment.

Methods

A population-based randomized controlled trial will be implemented in Portuguese urban and rural areas. Women eligible for cervical cancer screening will be randomized (1:1) to intervention and control. In the intervention group, women will be invited for screening through text messages, automated phone calls, manual phone calls and health professional appointments, to be applied sequentially to participants remaining non-adherent after each step. Control will be the current standard of care (invitation by written letter). The primary outcome is the proportion of women adherent to screening after step 1 or sequences of steps from 1 to 3.

The secondary outcomes are: proportion of women screened after each step (1a, 2 and 3); proportion of text messages/phone calls delivered; proportion of women previously screened in a private health institution who change to organized screening. The intervention and control groups will be compared based on intention-to-treat and per protocol analyses.

Ethics and dissemination

The study was approved by the Ethics Committee of the Northern Health Region Administration and the National Data Protection Committee. Results will be disseminated through communications in scientific meetings, peer-reviewed journals, and technical reports.

Trial registration number

NCT03122275

Number of Words: 3312

Key Words

Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

STRENGTHS OF THIS STUDY

- Randomized controlled trial, using a stepwise approach, with increasing complexity and cost of interventions, to improve adherence to organized cervical cancer screening
- Interventions tested are technological and innovative
- Use of a population approach and not specific groups or minorities

LIMITATIONS OF THIS STUDY

- Contamination of interventions may occur, because randomization units are individuals and not primary care units
- Unavailability of women's mobile phone may restrict intervention delivery

INTRODUCTION

Cancer is one of the most important causes of morbidity and mortality, especially in developed countries.(1) A substantial part of cancer cases can be detected earlier and undergo treatment with curative intent.(2) Improvements in early detection of cancer may be achieved through increases in population awareness, enabling early consultation with health professionals, and screening programs.(2) Cervical cancer screening is one of the oldest and most effective screening programs, with relevant decreases in mortality since its implementation.(3) Additionally, Human Papilloma Virus (HPV) vaccination started to be implemented for women younger than 26 years old, contributing to cancer prevention.(4) Although it is expected that the vaccine becomes widely implemented, screening will still be needed, at least for non-vaccinated women and high risk groups. This change of paradigm will reduce the number of eligible women for screening, so variable costs (invitation and screening) need to be reduced to guarantee sustainability.

Different strategies to increase adherence while reducing the cost of cervical cancer screening have been developed and evaluated, including interventions based on patient reminders (written letters(5–10), operator dependent phone calls(8,9,11,12) or text messages(13)), small media(14–17) (videos, brochures, pamphlets or fact sheets), mass media(18) and face-to-face educational programs(17,19).

Results from a systematic review(20) show overall increases in cervical cancer screening adherence of just over 10% with printed or phone reminders, and 4% and 8% when using small media or one-on-one education, respectively. Regarding the strategies based on the use of reminders, phone calls are more effective and cost-effective (37% uptake, costing 67$/response) than text messages (24% uptake, costing 100$/response) or written letters (19% uptake, costing 133$/response).(13) To our knowledge, no automated (machine performed) and customized phone calls have been used or compared with other methods.

Additionally, text messages have been tested as cervical cancer screening reminders or invitation methods (13), but with no patient customization or built-in mechanisms for reply to the messages. However, this method has been evaluated as appointment reminders in hospitals(21) and primary care health services(22), but also as part of chronic disease management programs, allowing for interaction with the patient(23).

Educational programs aiming to increase adherence to cervical cancer screening have been implemented using face-to-face interventions with trained professionals(17,19), sometimes using support videos or pamphlets(17). These programs are highly tailored to each patient, and therefore difficult to implement at a population level, because these are resource-intensive activities. In a population-based approach, a multistage intervention is needed, implementing first, cheaper and easier to use interventions such as text messages and automated phone calls. Women's refractory to these strategies should receive more expensive and patient tailored interventions such as phone calls performed by trained professionals as reminders or face-to-face appointments to provide information on cervical cancer screening. Most of the interventions described in the literature target only deprived populations(5,12,15) or from an ethnic group/social minorities(12,15,16,24) and only a few cases use multistage approaches (8,15).

Objectives

The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organized cervical cancer screening, in relation with the standard of care (invitation by written letter), implemented through three steps:

Step 1a – customized text message invitation;

Step 1b – customized automated phone call invitation;

Step 2 – secretary phone call;

Step 3 – health professional phone call and face-to-face appointment.

As primary objectives, we intend to test the superiority of the intervention based on step 1 (1a+1b), and multistage interventions based on steps 1 and 2, and steps 1 to 3.

The secondary objectives will be the following:

1. To test the non-inferiority of interventions based on step 1a and step 1 (1a+1b), considering a non-inferiority limit of 5%;
2. To test the superiority of the specific components of the multistage intervention corresponding to step 2 and step 3;
3. To quantify the differences in adherence to cervical cancer screening, for the intervention based on step 1 (1a+1b) and multistage interventions based on steps 1 and 2, and steps 1 to 3, between: a) Urban and rural areas; b) Younger and older populations; c) Deprived and non-deprived populations; d) Never vs. ever users of organized screening; e) History of regular vs. irregular participation in organized screening programs.

4. To quantify the differences in adherence to cervical cancer screening when using a positive or a neutral content of text messages and automated phone calls, in step 1.
5. To estimate the proportion of women who were undergoing performing cervical cancer screening in private health care services who started to be screened in an organized cervical cancer screening program, after a health professional face-to-face appointment at their primary care unit.

Intention-to-treat analysis will be used as primary strategy for all comparisons between interventions and control. Secondary per-protocol analysis will also be conducted.

METHODS AND ANALYSIS

Setting

The study will be conducted among women with a medical registration at two primary health care units in the north of mainland Portugal, namely *Porto Ocidental*, serving densely populated urban areas near the coast, and *Marão e Douro Norte*, located inland, covering scarcely populated and predominantly rural areas. These were selected because they have low adherence to cervical cancer screening.(25)

Design

This investigation is based on a population-based randomized controlled trial, with a parallel design, as depicted in Figure 1.

Women eligible for cervical cancer screening will be randomized 1:1 within each primary health care unit.

The intervention will comprise invitation to screening, through the following sequential steps:

Step 1 – Automated text messages (step 1a)/automated phone calls (step 1b);

Step 2 – Manual phone calls performed by secretaries, implemented one to two months after step 1, among women remaining non-adherent one month after step 1;

Step 3 – Health professional phone call and appointments, implemented one to two months after step 2, among women remaining non-adherent one month after step 2.

Intervention stops whenever the participants adhere to organized screening or after undergoing the whole intervention. Control will be the standard of care (invitation by written letter).

---------- INSERT FIGURE 1 HERE ----------

Participants

Inclusion criteria:

a) Women aged between 25 and 49 years, and eligible for cervical cancer screening (having started sexual activity, not hysterectomized, not undergoing cervical cancer treatment);

b) Medical registration at any of the primary health care units selected for this study;

Exclusion criteria:

No mobile phone number available at the National Health Service database.

Intervention

The intervention comprises different strategies for invitation to cervical cancer screening, to be applied sequentially, in three steps.

Step 1 (1a + 1b) – Automated text messages/phone calls

Women randomized to the intervention arm will be assigned a date and hour for screening by the primary health care unit secretaries, who will then upload the women's phone number, first and last name, name of the primary care unit and appointment date/hour in the software selected for implementation of step 1: File2Mail v.2.2, Smart IVR v.1.1, Smart Message v.3.1 and Speech2Go v.1.1. Personalized text messages (Step 1a), with a maximum length of 320

characters, and phone calls (Step 1b), with a maximum duration of 30 seconds, will then be automatically assembled and sent to the study participants.

When a screening invitation is accepted, either in step 1a or step 1b, a text message reminder will be sent to women 24-48h before the appointment (Text Box 1 – reminder message).(22)

Step 1a – Automated text messages

Two models of invitation text message will be randomized 1:1 within each primary health care unit (Text Box 1); invitation message 1 has a neutral style (close to the usual written invitation letter) and invitation message 2 has a gain-frame and positive style of writing.(26) The content validity of the invitation messages was tested among a few potentially eligible women, and modifications implemented as needed.

Women are asked to confirm their interest to undergo cervical cancer screening at the proposed date and time, answering the invitation with a text message saying "CONFIRM". If they do not confirm within 24 hours, they will additionally receive an automated phone call (step 1b).

Step 1b – Automated phone calls

A phone call invitation will be performed in after-hours period (17-20h), using a humanized female voice, and follows the same structure of the text messages (Figure 2 and Text Box 1– invitation phone call 1 and 2). Women will receive phone call 1 if they do not answer the invitation message 1 and receive phone call 2 if they did not answer the invitation message 2.

Women are asked to press the number 1 for appointment confirmation or the number 2 if they want to receive a phone call from the primary care unit secretary. The audio message will be repeated three times in the same call, or until women provide the feed-back required.

If women do not answer the phone call or do not press the number 1 or 2, a new automated phone call will be scheduled for the next day, for a maximum of three days (Figure 2).

---------- INSERT FIGURE 2 HERE ---------- ----------

---------- INSERT TEXT BOX 1 HERE ---------- ----------

Step 2 – Secretary phone call

Women who do not confirm the appointment in step 1 or do not attend organized cervical cancer screening are enrolled in step 2. This comprises an invitation phone call performed in after-hours period (17-20h), by the secretary of the corresponding primary care unit. Secretaries will be trained by the research team and will follow a predefined script (Appendix 1). If women do not answer the call, it will be repeated daily, for a maximum of three days. A date and hour for cervical cancer screening will be scheduled for women who agree to participate.

Step 3 – Health professional phone call and face-to-face appointment

Women who do not answer the phone during step 2, or do not participate in organized cervical cancer screening after the scheduled appointment, will be enrolled in step 3. This comprises a phone call and a face-to-face appointment performed by a health professional from the primary care unit (family nurses or resident medical doctors), specifically trained for this step of the intervention. Phone calls will be performed in after-hours period (17-20h), aiming to schedule an appointment, using a predefined script (Appendix 2). If women do not answer the call, it will be repeated daily, for a maximum of three days. During appointments, screening will be described and doubts clarified using the standard North Portugal cervical cancer screening pamphlet. Health professional will identify possible barriers felt by women and will try to overcome them using predefined arguments (Appendix 3). Additionally, women who agree to participate will be screened after the interview or scheduled for another date, defined according to their and the Service's convenience.

Outcomes

The primary outcome is defined as follows:

Adherence to cervical cancer screening

Proportion or cumulative proportion of women who performed cervical cancer screening on the scheduled date, among those who were invited, after step 1 or sequences of steps from 1 to 3, as applicable.

The secondary outcomes are defined as follows:

Adherence to cervical cancer screening (steps 1a, 2 and 3)

Proportion of women who performed cervical cancer screening on the scheduled date, among those who were invited, after step 1a, after step 2 or after step 3.

Text message status

Proportion of text messages received with confirmation, from those that were sent.

Automated phone call status

Proportion of automated phone calls delivered, from those that were attempted.

Change from opportunistic to organized screening

Proportion of women undergoing opportunistic cervical cancer screening in a private health institution who change to organized cervical cancer screening.

Adherence to text message invitation, secretary phone calls and written letters will be determined on the day after the scheduled appointment. Adherence to screening after health professional face-to-face interviews will be determined two months after the intervention.

Sample Size

Sample size was estimated considering the use of two-sided tests, for a significance level of 5% and a statistical power of 90%, intending the comparison of intervention and control groups regarding the outcomes defined as part of the primary objective.

Step 1 (1a+1b)

We estimate an adherence to screening based on invitation through a written letter of 40% (based on SiiMA Rastreios *software:* Portuguese software for cancer screening), and we intend to detect an increase to 50% with the intervention based on step 1. This 10% increase is expected because two different techniques of invitation will be used (text message and automated phone call) and an electronic reminder will be sent 24h prior to the appointment.(20) The minimum sample size determined for each group is 519 women.

Steps 1 and 2

We expect a 45% cumulative adherence proportion in the control group, after the interventions based on steps 1 and 2. This low increase is anticipated because no other interventions are performed. We intend to detect a cumulative adherence proportion of 60% in the intervention group. This increase is conservative, considering the published effectiveness of phone calls.(8,9) The minimum sample size determined for each group is 244 women.

Steps 1 to 3

We expect 50% and 70% cumulative adherence proportion in the control and intervention groups, respectively after the interventions based on steps 1 to 3. This increase in the

intervention group is expected according with published effectiveness of face-to-face appointments.(17) The minimum sample size determined for each group is 134 women.

The overall sample size needed per group is 519, determined by step 1 interventions, since the remaining primary outcomes require a smaller sample size. Nevertheless, a 10% greater number of participants will be recruited to account for the potential withdrawal of one health care unit before the completion of the stepwise intervention.

Regarding the calculated sample size, we have power to test the superiority of the isolate effect of step 2 or step 3, considering the expected proportion of women undergoing step 2 and step 3 interventions. Additionally, the sample size is also enough to test non-inferiority secondary objectives, assuming one-sided tests, a significance level of 2.5%, power of 90%, an adherence proportion in control group of 40% and 50% in experimental group and a non-inferiority limit of 5%.

Randomization

Women will be randomized 1:1 into the intervention or control groups (Figure 1). A woman randomized to the intervention or control will belong to that study arm until the end of the study. Primary care units will extract a list of eligible women for screening, fulfilling study criteria, from SiiMA Rastreios *software* (national software for cancer screening eligibility). Eligible women will be randomized using Excel v.Office 365.

If a woman is randomized to the intervention group, she will be randomized again to receive a neutral or a positively framed invitation text message/automated phone call on a 1:1 ratio (Figure 2).

Contamination is possible because women exposed to interventions may live geographically near women belonging to the control group, and therefore the participation of women from the intervention arm may influence the adherence of women in the control group. Although this is a possibility, we expect a limited effect on the results, because women in the intervention or control group may access cervical cancer screening at their primary care units for free. Zip-code randomization would contribute to minimize contamination, but it would not be feasible due to the unavailability of complete zip-codes on SiiMA Rastreios. We did not opt for randomization of primary care units because the number of randomization units available is low.

Data collection

Information about adherence to cervical cancer screening after interventions or standard of care (invitation letter) will be obtained using the national software for cancer screening eligibility – SiiMA Rastreios. This platform will also be used to collect data about women's previous participation in cervical cancer screening.

Patient appointment confirmation obtained from text messages and phone calls will be saved directly by the software into the study laptop database.

Sociodemographic characteristics will be manually extracted from the electronic medical record (EMR).

All the information written in the database will be pseudo-anonymized, using a unique identifier and only the principal investigator will have the encryption key. Only members of the research team will have access to the database. All medical data will be collected from EMR by medical doctors belonging to the research team.

Statistical analysis

Intention-to-treat analysis will be used as the primary strategy for all comparisons between interventions and control. Two secondary per-protocol analyses will also be conducted, considering only sub-groups of women, described as follows: a) women who received cervical cancer screening invitation (written letters or text message/phone call), b) women who confirm the appointment in the experimental arm and all women who received a written letter in the control arm.

Adherence proportions will be determined for step 1a, step 1b, step 1a+1b, step 2, step 3, and sequences of steps from 1 to 3. Differences of adherence proportions between the intervention and control groups will be tested using Qui-squared test or Fisher exact test as appropriate. Binary logistic regression may be used to control for confounding, or in secondary analyses of the isolate effects of steps 1b, 2 and 3. Performing the screening or not will be considered as the dependent variable and as independent variables, the study arm, age, education, marital status, number of children, previous adherence to cervical cancer screening and deprivation index.

Additionally, a stratified analysis will be performed, using as strata variables age (high vs. low), rurality (rural vs. urban), deprivation (deprived vs. non-deprived), regularity of previous participation (regular vs. irregular participation) and previous participation (ever vs. never participation).

Missing data is expected to be low for all the variables obtained from medical records, because they are collected on a regular basis by all general practitioners during appointments, using a structured entry form. No imputation of missing data is being planned.

All tests are two-tailed, with a p-value of 0.05 indicating statistical significance for superiority objectives or one-tailed with a p-value of 0.025 for non-inferiority objectives.

Ethics and dissemination

This study was approved by Portuguese regional ethics committee – *Comissão de Ética da Administração Regional de Saúde do Norte* (number: 20/2017) and by National Data Protection Committee (number: 11467/2016). The trial was registered and assigned the number NCT03122275.

For step 1 interventions (automated text messages/phone calls) obtaining an informed consent is not feasible, however, we consider that the benefits for participants and society outweigh the ethical aspects raised and the ethics committee recognized it. Women participating or not will not influence access and type of health care provided.

In steps 2 and 3, the secretaries or health professionals will explain the study and obtain verbal informed consent during the phone calls. In step 3, the health professionals will obtain written informed consent from all participants undergoing this step of the intervention.

All the software used to perform automated text messages and phone calls follow the Health Insurance Portability and Accountability Act (HIPAA) protocol and article number 8 of the European Convention of Human Rights.

A manuscript addressing the primary objective of this trial will be submitted for publication in a peer-reviewed journal. Additional manuscripts will be submitted for publication, intending to answer the secondary objectives. Communications in national and international scientific meetings are also expected. Technical reports will be made available to the primary care units and institutions involved in this study.

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OTHER INFORMATION

Trial registration

Trial identifier: NCT03122275 (registered on Clinical Trials.gov)

Registry name: Stepwise Strategy to Improve CANcer Screening Adherence: Cervical Cancer (SCAN-CC)

Protocol version

11 April 2017. 1st protocol version

Roles and responsibilities

João Firmino-Machado

Protocol responsibilities: Conceptual design of the research project, drafted the first version of the protocol manuscript and final manuscript production.

Study implementation responsibilities: Responsible for study presentation and enrolment of all primary care units, intervention implementation, data collection and analysis, and manuscript writing.

Romeu Mendes

Protocol responsibilities: Conceptual design of the research project and critical review of the manuscript.

Study implementation responsibilities: Responsible for study presentation and enrolment of the primary care units from ACeS Marão e Douro Norte, intervention implementation and data collection.

Amélia Moreira

Protocol responsibilities: Conceptual design of the research project and critical review of all protocol drafts.

Study implementation responsibilities: Responsible for study presentation and enrolment of the primary care units from ACeS Porto Oriental, intervention implementation.

Nuno Lunet

Protocol responsibilities: Conceptual design of the research project and critical review of all versions of the manuscript.

Study implementation responsibilities: Responsible for the supervision of the study implementation, data collection and analysis, and writing of the manuscripts.

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Name and contacts of funding institutions

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Henrique Barros, head of ISPUP: hbarros@med.up.pt

This is an academic trial that is supported both by the academic and the primary care institutions involved. Although the members of the research team belong to these institutions, the latter will not interfere in data analysis, results interpretation and decision to submit the manuscripts for publication.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no organisation influenced the authors about the decision to submit for publication the current work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Transparency declaration:

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been registered.

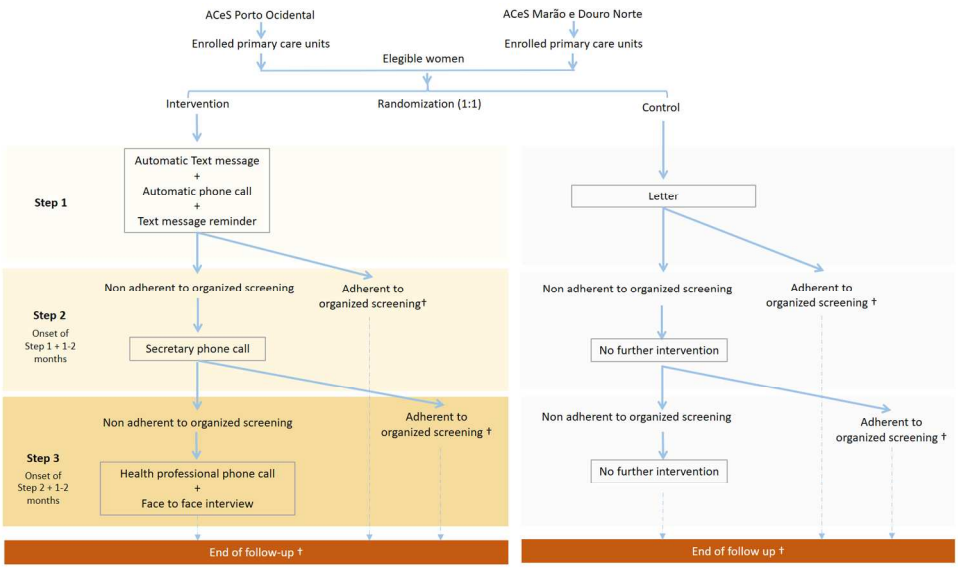
Figures

Legend: † - outcome assessment

Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.

Figure 2 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

Text Box 1 – Content for text messages and phone calls



Legend: † - outcome assessment

Title: Figure 1 - Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.

402x231mm (120 x 120 DPI)

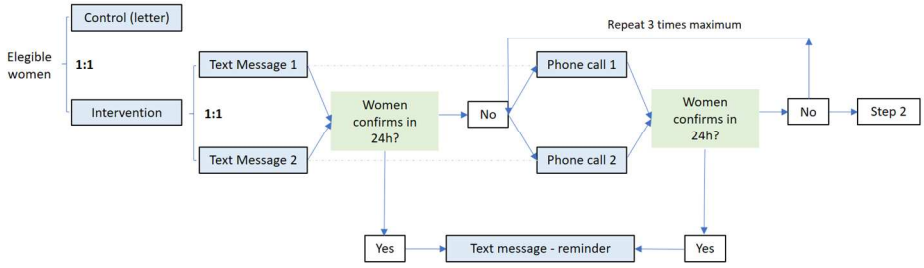


Figure 2 - Flow of Step 1 interventions: written letter, text messages and automated phone calls.

359x135mm (120 x 120 DPI)

Text Box 1 - Content for text messages and phone calls

Invitation message 1 (neutral framed)

[FIRST NAME] [LAST NAME]

This message is an invitation for cervical cancer screening (Papanicolaou), at your primary care unit [PRIMARY CARE UNIT NAME]

Your appointment is scheduled for [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free

Answer to this message with the word CONFIRM, to schedule the appointment

Invitation message 2 (positively framed)

[FIRST NAME] [LAST NAME]

Keep your cervical cancer screening updated (*Papanicolaou*)

Perform your screening appointment at your primary care unit [PRIMARY CARE UNIT NAME], on [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.

Answer to this message with the word CONFIRM, to schedule the appointment

Invitation phone call 1 (neutral framed)

Good evening [FIRST NAME] [LAST NAME], we are calling from your primary care unit [PRIMARY CARE UNIT NAME].

This call is an invitation for cervical cancer screening, using a Papanicolaou test.

Your appointment is scheduled for [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.

If you are available to attend this appointment press your phone number 1.

If you intend to be contacted by your primary care secretary press phone number 2.

Invitation phone call 2 (positively framed)

Good evening [FIRST NAME] [LAST NAME], we are calling from your primary care unit [PRIMARY CARE UNIT NAME].

You have the opportunity to update your cancer screening, using Papanicolaou.

We invite you to perform the screening at your primary care unit on [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.

If you are available to attend this appointment press your phone number 1.

If you intend to be contacted by your primary care secretary press phone number 2.

Reminder message

[FIRST NAME] [LAST NAME]

Your cervical cancer screening (Papanicolaou) is scheduled for tomorrow [DATE: DD-MM-YYYY], [HOURS: HH:MM], at your primary care unit [PRIMARY CARE UNIT NAME]

Text Box 1 – Content for text messages and phone calls

405x229mm (120 x 120 DPI)

Appendix 1 – Secretary and health professional phone call protocol

Secretary and health professional phone call structure

Follow this interview model when calling women enrolled in the current research study.

Operator: Good evening, my name is [SECRETARY OR HEALTH PROFESSIONAL NAME]. I am calling from [PRIMARY HEALTH CARE CENTER NAME]. Am I speaking with [WOMAN´S NAME]?

Action: If yes, the interview continues. If no, ask to speak with her. If it is the wrong number, politely end the phone call and hang up.

Operator: I am calling because you do not have an updated cervical cancer screening that is performed using the Papanicolaou test. This phone call is performed in the context of a research project and your participation is voluntary. Would it be possible to speak with you for one minute about the cervical cancer screening?

Action: If yes, the interview continues (Section 1 or 2, depending on if you are a secretary or a health professional). If no, politely end the phone call and hang up.

- - - - - *Skip to **Section 1** if you are a secretary or to **Section 2** if you are a health professional* - -

Section 1 – Continue from here if you are a secretary

Operator: Can I schedule an appointment at your primary care unit [NAME OF YOUR PRIMARY CARE UNIT], to perform a Papanicolaou test, to update your cervical cancer screening program?

Action: If yes, the appointment is scheduled and the phone call is ended. Give additional information about the location of the primary care unit if this is needed. If no, politely end the phone call and hang up.

END

Section 2 – Continue from here if you are a health professional

Operator: I would like to speak with you about cervical cancer screening. Is it possible we schedule an appointment at your primary care unit [PRIMARY CARE UNIT NAME]?

Action: If yes, an appointment is scheduled and the phone call is ended. Give extra information about primary care unit location if it is needed. If not, end up the interview.

END

Appendix 2 – Health professional face-to-face interview

Health professional face-to-face interview

The following guide will be used for health professionals, to implement face-to-face appointments.

1 – Invite woman into a quiet and comfortable room, with no other patients, inside the primary care unit.

2 – Present the study protocol and invite woman to participate.

Action: If woman refuses, the interview ends. If woman accepts the interview continues and an informed consent is signed.

3 – Ask woman the motive(s) for non-adherence to cervical cancer screening.

Action: Use the table from appendix 3 to adapt the motive(s) for non-adherence to the possible motives listed. Use the arguments in the table to answer.

4 – Ask if there are any more doubts and clarify them if necessary.

5 – Ask if you could present the pamphlet of cervical cancer screening.

Action: If no, skip this step. If yes, present the document and highlight each section. Ask the woman if she would like to know more about any of the sections or has any specific doubts about them. Answer all questions and clarify any information if needed.

6 – Invite woman to be screened today (if the institution has the capability of performing the exam) or another day and define the date and time.

Action: If a woman refuses screening, thank her for all the time dispended and tell her that she can come again to talk about cervical cancer screening. If a woman accepts, screening is scheduled.

END

Appendix 3 – Potential barriers to cervical cancer screening and tools to overcome them during health professional appointments.

Barrier	Barrier description	Approach
Economic barriers	Amount needed to be paid to perform the screening.	Screening appointments and pap tests are free of charge (1).
Accessibility	Difficulties in scheduling an appointment. Location of screening is difficult to access.	Screening is performed at your primary care unit between Monday to Friday, from 8AM to 8PM.
Screening process	Previous negative experiences when undergoing the Papanicolaou test; namely pain, discomfort or constraint. Professional who performs the screening.	a) The pap test in not painful for most women. Even those who feel pain classify it only as slight. (2) b) You may ask for another medical professional to perform the pap test (female doctor if your doctor is male). c) You can bring someone from your family or a friend on the screening day.
Screening exam characteristics	Sensitivity, specificity. Perception that is not adequate/best exam.	Cervical cancer screening methods have evolved, with increased performance on detection of pre-malignant or malignant lesions. Currently, screening has the following characteristics: a) Liquid-based cytology with automatic reading of results is currently implemented and, if necessary. additional HPV tests are performed (1,3). b) Sensitivity and specificity are 76 and 89%, respectively, for this screening methodology (4).
Fear of	Fear of detecting a malignant lesion and possible need	a) High income countries which have implemented cervical cancer screening, have reduced cervical

cancer/treatment	to undergo treatment.	cancer mortality by 80% and have also reduced the occurrence of new cases of the disease (4). b) Only 6.2% of all pap tests have an abnormal result (5). c) The most common abnormal result is ASC-US (3.5% of pap tests performed) which corresponds to benign cases requiring only annual follow up (5). d) The most uncommon abnormal result is HSIL (<1% of all results). From these abnormal results, 1-4% will have an invasive carcinoma (3,5). e) Screening allows early detection of cervical cancer, more attempted treatment and better prognosis. (6)
Screening indication	Women do not perceive they are at risk, because they are too young to start screening or they do not have symptoms.	All women aged between 25 and 60 are recommended to undergo cervical cancer screening every 5 years, except if they (1): - Are being treated for cervical cancer - Are hysterectomized - Have not initiated sexual activity - Physical limitation that does not allow a pap test to be performed - Presence of signals or symptoms of gynaecologic disease (active)
Preference for private health care services	Women prefer to be screened in a private institution, e.g.: by a gynaecologist versus a family doctor	Advantages of an organized cervical cancer screening program (6): a) Higher technical skills and experience of laboratory professionals who read results and classify them b) Frequent quality control verifications c) Standardization of technical procedures

1. Departamento de Estudos e Planeamento - ARS Norte. Manual de procedimentos do rastreio do cancro do colo do útero 2009; Available from: www.arsnorte.min-saude.pt

2. Simavli S, Kaygusuz I, Kmay T, Cukur S. The role of gel application in decreasing pain during speculum examination and its effects on papanicolaou smear results. Arch Gynecol Obs 2014;289: 809–15.

3. Sociedade Portuguesa de Ginecologia. Consenso sobre infeção por HPV e neoplasia intraepitelial do colo, vulva e vagina 2014; 1-96.

4. IARC. Handbooks of Cancer Prevention, in: vol10, chapter 4. 2005; 163–99.

5. Raquel M, Bastos A de. Prevalência da Infecção por HPV num Grupo de Mulheres Portuguesas. Biochemistry Master Thesis 2011.

6. WHO. Cancer Control - Early detection 2007; 1–50.

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)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	7,8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	not applicable
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	not applicable
Sample size	7a	How sample size was determined	15,16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	17
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	17
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	17
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	17
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	17

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	19
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	19
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	not applicable (study is a protocol)
	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable (study is a protocol)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable (study is a protocol)
	14b	Why the trial ended or was stopped	not applicable (study is a protocol)
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable (study is a protocol)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	not applicable (study is a protocol)
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)	not applicable (study is a protocol)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable (study is a protocol)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	not applicable (study is a protocol)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable (study is a protocol)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable (study is a protocol)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable (study is a protocol)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable (study is a protocol)

Other information			
Registration	23	Registration number and name of trial registry	25
Protocol	24	Where the full trial protocol can be accessed, if available	not applicable (study is a protocol)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	27

*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.

BMJ Open

Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCAN-CC) – Automated Text Messages, Phone Calls and Face-to-face Interviews: Protocol of a population based randomized controlled trial

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Keywords:	Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

TITLE PAGE

Title: Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCAN-CC) – Automated Text Messages, Phone Calls and Face-to-face Interviews: Protocol of a population based randomized controlled trial

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ABSTRACT

Introduction

Screening is highly effective for cervical cancer prevention and control. Population based screening programs are widely implemented in high income countries, though adherence is often low. In Portugal, just over half of the women adhere to cervical cancer screening, contributing for greater mortality rates than in other European countries. The most effective adherence raising strategies are based on patient reminders, small/mass media and face-to-face educational programs, but sequential interventions targeting the general population have seldom been evaluated.

The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organized cervical cancer screening: step 1a-customized text message invitation;step 1b-customized automated phone call invitation;step 2-secretary phone call;step 3-family health professional phone call and face-to-face appointment.

Methods

A population-based randomized controlled trial will be implemented in Portuguese urban and rural areas. Women eligible for cervical cancer screening will be randomized(1:1) to intervention and control. In the intervention group, women will be invited for screening through text messages, automated phone calls, manual phone calls and health professional appointments, to be applied sequentially to participants remaining non-adherent after each step. Control will be the standard of care(written letter). The primary outcome is the proportion of women adherent to screening after step1 or sequences of steps from 1-3.

The secondary outcomes are: proportion of women screened after each step(1a,2 and 3); proportion of text messages/phone calls delivered; proportion of women previously screened in a private health institution who change to organized screening. The intervention and control groups will be compared based on intention-to-treat and per protocol analyses.

Ethics and dissemination

The study was approved by the Ethics Committee of the Northern Health Region Administration and National Data Protection Committee. Results will be disseminated through communications in scientific meetings and peer-reviewed journals.

Trial number:NCT03122275

Number of Words: 3312

Key Words

Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

STRENGTHS OF THIS STUDY

- Randomized controlled trial, using a stepwise approach, with increasing complexity and cost of interventions, to improve adherence to organized cervical cancer screening
- Interventions tested are technological and innovative
- Use of a population approach and not specific groups or minorities

LIMITATIONS OF THIS STUDY

- Contamination of interventions may occur, because randomization units are individuals and not primary care units
- Unavailability of women's mobile phone may restrict intervention delivery
- The study is restricted to women aged below 50 years, and therefore the findings may not apply to older women with limited digital literacy skills

INTRODUCTION

Cancer is one of the most important causes of morbidity and mortality, especially in developed countries.(1) A substantial part of cancer cases can be detected earlier and undergo treatment with curative intent.(2) Improvements in early detection of cancer may be achieved through increases in population awareness, enabling early consultation with health professionals, and screening programs.(2) Cervical cancer screening is one of the oldest and most effective screening programs, with relevant decreases in mortality since its implementation.(3) Although the increasing coverage of vaccination against high-risk Human Papillomavirus (HPV) strains is expected to play a major role in the prevention of cervical cancer(4), screening will still be needed, at least for non-vaccinated women and high risk groups. With the expected decrease in the number of women eligible for screening, cost reduction, including variable costs (invitation and screening), may be needed to guarantee sustainability.

Currently, in Portugal cervical cancer screening is recommended to be performed every 5 years, for women aged between 25 and 65 years old(5). Women registered at a primary care unit are invited to perform cervical cancer screening through a written letter. At a national level, just over half(5) of the invited women adhere to the cervical cancer screening and 23.5%(6) have never performed screening during life. Limited adherence to screening is expected to contribute to greater cervical cancer mortality rates in Portugal (age-standardized mortality rate: 4.9/100.000)(7), in comparison with the average in Europe's rate (27 countries, age-standardized mortality rate: 3.7/100.000)(7).

Different strategies to increase adherence to cervical cancer screening have been developed and evaluated, including interventions based on patient reminders (written letters(8–13), operator dependent phone calls(11,12,14,15) or text messages(16)), small media(17–20) (videos, brochures, pamphlets or fact sheets), mass media(21) and face-to-face educational programs(20,22).

Results from a systematic review(23), including studies conducted in high income countries, enrolling both deprived and non-deprived women, show overall increases in cervical cancer screening adherence of just over 10% with printed or phone reminders, and 4% and 8% when using small media or one-on-one education, respectively. Regarding the strategies based on the use of reminders, phone calls are more effective and cost-effective (37% uptake, costing 67$/response) than text messages (24% uptake, costing 100$/response) or written letters (19% uptake, costing 133$/response)(16). To our knowledge, no automated (machine performed) and customized phone calls have been used or compared with other methods. Additionally, text messages have been tested as cervical cancer screening reminders or invitation methods (16), but with no patient customization or built-in mechanisms for reply to the messages. This method was tested as appointment reminders in hospitals (24) and primary health care health services(25), with 10% increases in adherence to scheduled appointments, but also as part of obesity control programs(26). Some of these programs allow for patient interaction, enabling them to make a data input on their health status or simply reply after receiving the intervention(26). This bi-directional approach, could be used for cancer screening invitation and appointment scheduling, by allowing the invited people to confirm their interest to be screened, using a text message or a reply to an automatic phone call. A recent systematic review on the use of automated telephone communication systems highlighted the effectiveness of unidirectional/bi-directional phone-delivered interventions on the uptake increase of screening programs(27).

Educational programs aiming to increase adherence to cervical cancer screening have been implemented using face-to-face interventions with trained professionals(20,22), sometimes using support videos or pamphlets(20) or delivered through motivational phone call(28). These programs are highly tailored to each patient, and therefore difficult to implement at a population level, because these are resource-intensive activities. In a population-based approach, a multistage intervention is needed, implementing first, cheaper and easier to use

interventions such as text messages and automated phone calls. Women refractory to these strategies should receive more expensive and patient tailored interventions such as phone calls performed by trained professionals as reminders or face-to-face appointments to provide information on cervical cancer screening. Most of the interventions described in the literature target only deprived populations(8,15,18) or from an ethnic group/social minorities(15,18,19,29) and only a few cases use multistage approaches, where different interventions (written letter invitation, written letter reminder, phone call reminder) were sequentially applied till women adhere to screening(8).

Objectives

The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organized cervical cancer screening, in relation with the standard of care (invitation by written letter), implemented through three steps:

Step 1a – customized text message invitation;

Step 1b – customized automated phone call invitation;

Step 2 – secretary phone call;

Step 3 – health professional phone call and face-to-face appointment.

As primary objectives, we intend to test the superiority of the intervention based on step 1 (1a+1b), and multistage interventions based on steps 1 and 2, and steps 1 to 3.

The secondary objectives will be the following:

1. To test the non-inferiority of interventions based on step 1a and step 1 (1a+1b), considering a non-inferiority limit of 5%;
2. To test the superiority of the specific components of the multistage intervention corresponding to step 2 and step 3;
3. To quantify the differences in adherence to cervical cancer screening, for the intervention based on step 1 (1a+1b) and multistage interventions based on steps 1 and 2, and steps 1 to 3, between: a) Urban and rural areas; b) Younger and older populations; c) Deprived and non-deprived populations; d) Never vs. ever users of organized screening; e) History of regular vs. irregular participation in organized screening programs.

4. To quantify the differences in adherence to cervical cancer screening when using a positive or a neutral content of text messages and automated phone calls, in step 1.
5. To estimate the proportion of women who were undergoing performing cervical cancer screening in private health care services who started to be screened in an organized cervical cancer screening program, after a health professional face-to-face appointment at their primary care unit.

Intention-to-treat analysis will be used as primary strategy for all comparisons between interventions and control. Secondary per-protocol analysis will also be conducted.

The current interventions intend to be inexpensive and easy to implement so they can be used both in high and low-income countries, at a population level, as strategies to increase the adherence to cervical cancer screening.

METHODS AND ANALYSIS

Setting

The study will be conducted among women with a medical registration at two primary health care areas in the north of mainland Portugal, namely *Porto Ocidental*, serving densely populated urban areas near the coast, and *Marão e Douro Norte*, located inland, covering scarcely populated and predominantly rural areas. These were selected because they have low adherence to cervical cancer screening: 32% for *Porto Ocidental* and 61% for *Marão e Douro Norte*).(30)

Design

This investigation is based on a population-based randomized controlled trial, with a parallel design, as depicted in Figure 1.

Women eligible for cervical cancer screening will be randomized 1:1 within each primary health care unit.

The intervention will comprise invitation to screening, through the following sequential steps:

Step 1 – Automated text messages (step 1a)/automated phone calls (step 1b);

Step 2 – Manual phone calls performed by secretaries, implemented one to two months after step 1, among women remaining non-adherent one month after step 1;

Step 3 – Health professional phone call and appointments, implemented one to two months after step 2, among women remaining non-adherent one month after step 2.

Intervention stops whenever the participants adhere to organized screening or after undergoing the whole intervention. Control will be the standard of care (invitation by written letter).

---------- INSERT FIGURE 1 HERE ----------

Participants

Inclusion criteria:

a) Women aged between 25 and 49 years, and eligible for cervical cancer screening (having started sexual activity, not hysterectomized, not undergoing cervical cancer treatment);

b) Medical registration at any of the primary health care units selected for this study;

Although cervical cancer screening programs are recommended for women with ages till 65 years, will only be considered those that are younger than 50 years because they are expected to have higher levels of digital literacy and higher use of mobile phones. Data from 2013 suggests that 99% of the population in the intended age group uses regularly a mobile phone in comparison with approximately 90% for older age groups(31).

Exclusion criteria:

No mobile phone number available at the National Health Service database.

Intervention

The intervention comprises different strategies for invitation to cervical cancer screening, to be applied sequentially, in three steps.

Step 1 (1a + 1b) – Automated text messages/phone calls

Women randomized to the intervention arm will be assigned a date and hour for screening by the primary health care unit secretaries, who will then upload the women's phone number, first and last name, name of the primary care unit and appointment date/hour in the software selected for implementation of step 1: File2Mail v.2.2, Smart IVR v.1.1, Smart Message v.3.1 and Speech2Go v.1.1. Personalized text messages (Step 1a), with a maximum length of 320 characters, and phone calls (Step 1b), with a maximum duration of 30 seconds, will then be automatically assembled and sent to the study participants.

When a screening invitation is accepted, either in step 1a or step 1b, a text message reminder will be sent to women 24-48h before the appointment (Text Box 1 – reminder message).(25)

Step 1a – Automated text messages

Two models of invitation text message will be randomized 1:1 within each primary health care unit (Text Box 1); invitation message 1 has a neutral style (close to the usual written invitation letter) and invitation message 2 has a gain-frame and positive style of writing.(32) The content validity of the invitation messages was tested among a few potentially eligible women, and modifications were implemented, namely the name of the primary care unit and information stating that the appointment has no co-payments was added to the original text message.

Women are asked to confirm their interest to undergo cervical cancer screening at the proposed date and time, answering the invitation with a text message saying "CONFIRM". If they do not confirm within 24 hours, they will additionally receive an automated phone call (step 1b).

Step 1b – Automated phone calls

A phone call invitation will be performed in after-hours period (17-20h), using a humanized female voice, and follows the same structure of the text messages (Figure 2 and Text Box 1–

invitation phone call 1 and 2). Women will receive phone call 1 if they do not answer the invitation message 1 and receive phone call 2 if they did not answer the invitation message 2.

Women are asked to press the number 1 for appointment confirmation or the number 2 if they want to receive a phone call from the primary care unit secretary. The audio message will be repeated three times in the same call, or until women provide the feed-back required.

If women do not answer the phone call or do not press the number 1 or 2, a new automated phone call will be scheduled for the next day, for a maximum of three days (Figure 2).

---------- INSERT FIGURE 2 HERE ---------- ----------

---------- INSERT TEXT BOX 1 HERE ---------- ----------

Step 2 – Secretary phone call

Women who do not confirm the appointment in step 1 or do not attend organized cervical cancer screening are enrolled in step 2. This comprises an invitation phone call performed in after-hours period (17-20h), by the secretary of the corresponding primary care unit. Secretaries will be trained by the research team and will follow a predefined script (Appendix 1). If women do not answer the call, it will be repeated daily, for a maximum of three days. A date and hour for cervical cancer screening will be scheduled for women who agree to participate.

Step 3 – Health professional phone call and face-to-face appointment

Women who do not answer the phone during step 2, or do not participate in organized cervical cancer screening after the scheduled appointment, will be enrolled in step 3. This comprises a phone call and a face-to-face appointment performed by a health professional from the primary care unit (family nurses or resident medical doctors), specifically trained for this step of the intervention. Phone calls will be performed in after-hours period (17-20h), aiming to schedule an appointment, using a predefined script (Appendix 2). If women do not answer the call, it will be repeated daily, for a maximum of three days. During appointments, screening will be described and doubts clarified using the standard North Portugal cervical cancer screening pamphlet. Health professional will identify possible barriers felt by women and will try to overcome them using predefined arguments (Appendix 3). Additionally, women who agree to participate will be screened after the interview or scheduled for another date, defined according to their and the Service's convenience.

Outcomes

The primary outcome is defined as follows:

Adherence to cervical cancer screening

Proportion or cumulative proportion of women who performed cervical cancer screening on the scheduled date, among those who were invited, after step 1 or sequences of steps from 1 to 3, as applicable.

The secondary outcomes are defined as follows:

Adherence to cervical cancer screening (steps 1a, 2 and 3)

Proportion of women who performed cervical cancer screening on the scheduled date, among those who were invited, after step 1a, after step 2 or after step 3.

Text message status

Proportion of text messages received with confirmation, from those that were sent.

Automated phone call status

Proportion of automated phone calls delivered, from those that were attempted.

Change from opportunistic to organized screening

Proportion of women undergoing opportunistic cervical cancer screening in a private health institution who change to organized cervical cancer screening.

The index dates for adherence assessment will be the following: 1) the day after the appointment date, for text message invitation, secretary phone calls and written letters; 2) two months after the intervention based on face-to-face interviews conducted by health professionals.

Sample Size

Sample size was estimated considering the use of two-sided tests, for a significance level of 5% and a statistical power of 90%, intending the comparison of intervention and control groups regarding the outcomes defined as part of the primary objective.

Step 1 (1a+1b)

We estimate an adherence to screening based on invitation through a written letter of 40% (based on SiiMA Rastreios *software:* Portuguese software for cancer screening), and we intend to detect an increase to 50% with the intervention based on step 1. We expect this 10% increase because two different techniques of invitation will be used (text message and automated phone call) and an electronic reminder will be sent 24h prior to the appointment.(23) The minimum sample size determined for each group is 519 women.

Steps 1 and 2

We expect a 45% cumulative adherence proportion in the control group, after the interventions based on steps 1 and 2; an increase in relation to the expected adherence in the control group after steps 1, from 40 to 45%, may be anticipated because for step 2 there will be a longer period between baseline and outcome assessment. We expect a cumulative adherence proportion of 60% in the intervention group, which is a conservative estimate, considering the published effectiveness of phone calls.(11,12) The minimum sample size determined for each group is 244 women.

Steps 1 to 3

We expect 50% and 70% cumulative adherence proportion in the control and intervention groups, respectively after the interventions based on steps 1 to 3. In the control group, an

increase in comparison to the expected adherence after steps 2, from 45 to 50%, may be anticipated due to the longer period between baseline and outcome assessment. The magnitude of increase in adherence in the intervention group, was estimated based on the previously observed effectiveness of face-to-face appointments in other settings.(20). The minimum sample size determined for each group is 134 women.

The overall sample size needed is 1038 (519*2), determined by step 1 interventions, since the remaining primary outcomes require a smaller sample size. Nevertheless, a 10% greater number of participants will be recruited to account for the potential withdrawal of one health care unit before the completion of the stepwise intervention. We anticipate that the drop-out of individual participants will be lower than 1%, during the steps 2 and 3 of the intervention; this low value is expected because we will use an opt-out strategy, so that only women who actively express their willingness for not receiving further interventions are considered as drop-outs.

The statistical analysis for accomplishment of secondary objectives are exploratory and therefore the sample size was not determined to consider them. Nevertheless, the sample size defined for the study, is expected to have enough power to test the superiority of the isolate effect of step 1b, step 2 or step 3. Additionally, the sample size is also enough to test non-inferiority secondary objectives, assuming one-sided tests, a significance level of 2.5%, power of 90%, an adherence proportion in control group of 40% and 50% in experimental group and a non-inferiority limit of 5%.

Randomization

Women will be randomized 1:1 into the intervention or control groups (Figure 1). A woman randomized to the intervention or control will belong to that study arm until the end of the study. Primary care units will extract a list of eligible women for screening, fulfilling study criteria, from SiiMA Rastreios *software* (national software for cancer screening eligibility). Principal investigator will generate the randomization sequence through Excel v.Office 365. All women registered and fulfilling eligibility criteria will be assigned to intervention or control by the primary care unit secretaries. If a woman is randomized to the intervention group, she will be randomized again to receive a neutral or a positively framed invitation text message/automated phone call on a 1:1 ratio (Figure 2). There will be no blinding of the participants, health professionals or elements of the research team.

Contamination is possible, especially because screening can be obtained for free in both groups and women exposed to interventions may live geographically near women belonging to control group. Therefore, the participation of women from the intervention arm may influence the adherence of women in the control group. Contamination will dilute the effect of the interventions to be tested, and all the effectiveness estimates computed will be conservative. Although we cannot accurately predict the magnitude of the impact of contamination, we may speculate that it will increase with the expected impact of interventions (with their increase in complexity), being higher for step 3 than for step 1. Zip-code randomization would contribute to minimize contamination, but it would not be feasible due to the unavailability of complete zip-codes on SiiMA Rastreios. We did not opt for randomization of primary care units because the number of randomization units available is low.

Data collection

Information about adherence to cervical cancer screening after interventions or standard of care (invitation letter) will be obtained using the national software for cancer screening eligibility – SiiMA Rastreios. This platform will also be used to collect data about women's previous participation in cervical cancer screening.

Patient appointment confirmation obtained from text messages and phone calls will be saved directly by the software into the study laptop database.

Sociodemographic characteristics, including age, education level, parity, marital and employment status, will be manually extracted from the electronic medical record (EMR).

All the information written in the database will be pseudo-anonymized, using a unique identifier and only the principal investigator will have the encryption key. Only members of the research team will have access to the database. All medical data will be collected from EMR by medical doctors belonging to the research team.

Statistical analysis

Intention-to-treat analysis will be used as the primary strategy for all comparisons between interventions and control. Two secondary per-protocol analyses will also be conducted, considering only the following subsets of participants:

a) women who receive the invitation

- experimental arm: women who receive a text message/phone call, as confirmed by the software used for automated delivery of the intervention

- control arm: women who received a written letter, *i.e.* no invitation letter returned

b) women who have an appointment scheduled:

- experimental arm: women who confirm the appointment by replying to the text message or automatic phone call invitation

- control arm: women assumed to have received the invitation letter with the appointment scheduled, *i.e.* letter not returned.

Adherence proportions will be determined for step 1a, step 1b, step 1a+1b, step 2, step 3, and sequences of steps from 1 to 3. Differences of adherence proportions between the intervention and control groups will be tested using chi-squared test or Fisher exact test as appropriate. Binary logistic regression may be used to control for confounding, or in secondary analyses of the isolate effects of steps 1b, 2 and 3. Adherence to screening will be considered as the dependent variable. Independent variables will include study arm and potential confounders selected among age, education, marital status, number of children, employment status, type of living area (rural vs. urban), previous adherence to cervical cancer screening and deprivation index.

Additionally, a stratified analysis will be performed, using as strata variables age (high vs. low), rurality (rural vs. urban), deprivation (deprived vs. non-deprived), regularity of previous participation (regular vs. irregular participation) and previous participation (ever vs. never participation).

Missing data is expected to be low for all the variables obtained from medical records, because they are collected on a regular basis by all general practitioners during appointments, using a structured entry form. No imputation of missing data is being planned.

All tests are two-tailed, with a p-value of 0.05 indicating statistical significance for superiority objectives or one-tailed with a p-value of 0.025 for non-inferiority objectives.

Ethics and dissemination

This study was approved by Portuguese regional ethics committee – *Comissão de Ética da Administração Regional de Saúde do Norte* (number: 20/2017) and by National Data Protection Committee (number: 11467/2016). The trial was registered and assigned the number NCT03122275.

For step 1 interventions (automated text messages/phone calls) obtaining an informed consent is not feasible, however, we consider that the benefits for participants and society outweigh the ethical aspects raised and the ethics committee recognized it. Women participating or not will not influence access and type of health care provided.

In steps 2 and 3, the secretaries or health professionals will explain the study and obtain verbal informed consent during the phone calls. In step 3, the health professionals will obtain written informed consent from all participants undergoing this step of the intervention.

All the software used to perform automated text messages and phone calls follow the Health Insurance Portability and Accountability Act (HIPAA) protocol and article number 8 of the European Convention of Human Rights.

A manuscript addressing the primary objective of this trial will be submitted for publication in a peer-reviewed journal. Additional manuscripts will be submitted for publication, intending to answer the secondary objectives. Communications in national and international scientific meetings are also expected. Technical reports will be made available to the primary care units and institutions involved in this study.

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OTHER INFORMATION

Trial registration

Trial identifier: NCT03122275 (registered on Clinical Trials.gov)

Registry name: Stepwise Strategy to Improve CANcer Screening Adherence: Cervical Cancer (SCAN-CC)

Protocol version

11 April 2017. 1st protocol version

Roles and responsibilities

All the authors of the manuscript follow the four criteria of authorship defined by ICMJE.

A description of responsibilities/author can be found below:

João Firmino-Machado

Protocol responsibilities: Conceptual design of the research project, drafted the first version of the protocol manuscript and final manuscript production.

Study implementation responsibilities: Responsible for study presentation and enrolment of all primary care units, intervention implementation, data collection and analysis, and manuscript writing.

Romeu Mendes

Protocol responsibilities: Conceptual design of the research project and critical review of the manuscript.

Study implementation responsibilities: Responsible for study presentation and enrolment of the primary care units from ACeS Marão e Douro Norte, intervention implementation and data collection.

Amélia Moreira

Protocol responsibilities: Conceptual design of the research project and critical review of all protocol drafts.

Study implementation responsibilities: Responsible for study presentation and enrolment of the primary care units from ACeS Porto Oriental, intervention implementation.

Nuno Lunet

Protocol responsibilities: Conceptual design of the research project and critical review of all versions of the manuscript.

Study implementation responsibilities: Responsible for the supervision of the study implementation, data collection and analysis, and writing of the manuscripts.

All the authors gave a final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Name and contacts of funding institutions

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This is an academic trial that is supported both by the academic and the primary care institutions involved. Although the members of the research team belong to these institutions, the latter will not interfere in data analysis, results interpretation and decision to submit the manuscripts for publication.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no organisation influenced the authors about the decision to submit for publication the current work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Transparency declaration:

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been registered.

Figures

Legend: † - outcome assessment

Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.

Figure 2 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

Text Box 1 – Content for text messages and phone calls

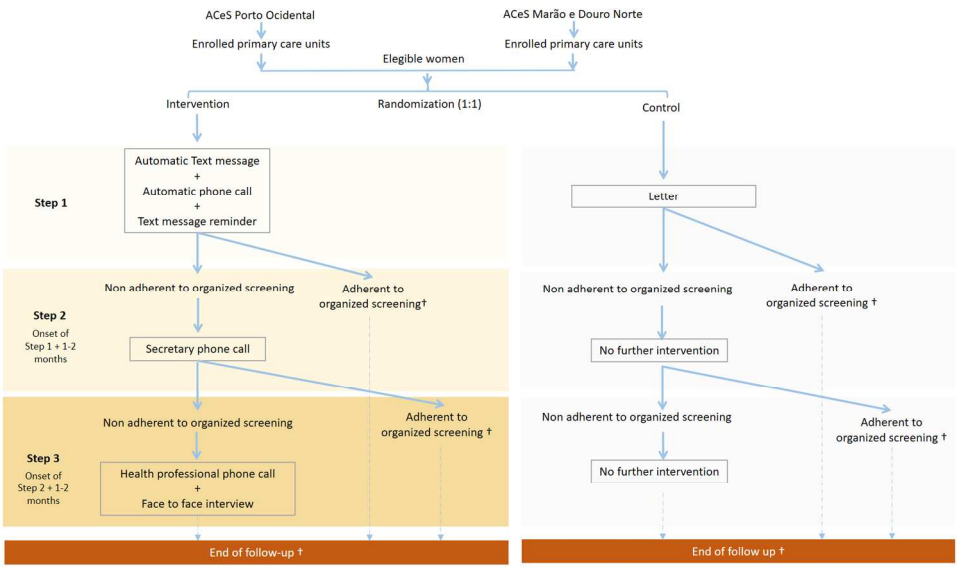

Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.
Legend: † - outcome assessment

402x231mm (300 x 300 DPI)

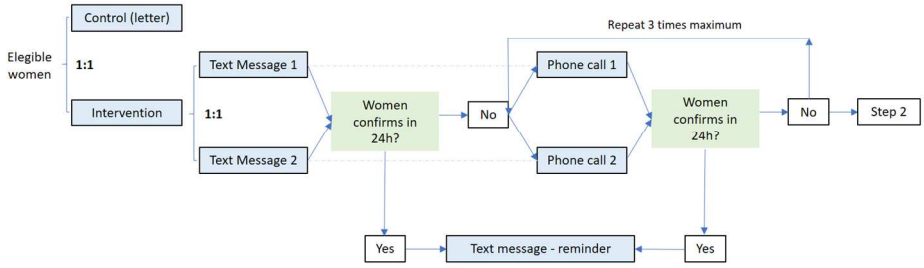

Figure 2 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

359x135mm (300 x 300 DPI)

Text Box 1 - Content for text messages and phone calls

Invitation message 1 (neutral framed)

[FIRST NAME] [LAST NAME]

This message is an invitation for cervical cancer screening (Papanicolaou), at your primary care unit [PRIMARY CARE UNIT NAME]

Your appointment is scheduled for [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free

Answer to this message with the word CONFIRM, to schedule the appointment

Invitation message 2 (positively framed)

[FIRST NAME] [LAST NAME]

Keep your cervical cancer screening updated (*Papanicolaou*)

Perform your screening appointment at your primary care unit [PRIMARY CARE UNIT NAME], on [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.

Answer to this message with the word CONFIRM, to schedule the appointment

Invitation phone call 1 (neutral framed)

Good evening [FIRST NAME] [LAST NAME], we are calling from your primary care unit [PRIMARY CARE UNIT NAME].

This call is an invitation for cervical cancer screening, using a Papanicolaou test.

Your appointment is scheduled for [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.

If you are available to attend this appointment press your phone number 1.

If you intend to be contacted by your primary care secretary press phone number 2.

Invitation phone call 2 (positively framed)

Good evening [FIRST NAME] [LAST NAME], we are calling from your primary care unit [PRIMARY CARE UNIT NAME].

You have the opportunity to update your cancer screening, using Papanicolaou.

We invite you to perform the screening at your primary care unit on [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.

If you are available to attend this appointment press your phone number 1.

If you intend to be contacted by your primary care secretary press phone number 2.

Reminder message

[FIRST NAME] [LAST NAME]

Your cervical cancer screening (Papanicolaou) is scheduled for tomorrow [DATE: DD-MM-YYYY], [HOURS: HH:MM], at your primary care unit [PRIMARY CARE UNIT NAME]

Text Box 1 – Content for text messages and phone calls

405x229mm (300 x 300 DPI)

Appendix 1 – Secretary and health professional phone call protocol

Secretary and health professional phone call structure

Follow this interview model when calling women enrolled in the current research study.

Operator: Good evening, my name is [SECRETARY OR HEALTH PROFESSIONAL NAME]. I am calling from [PRIMARY HEALTH CARE CENTER NAME]. Am I speaking with [WOMAN´S NAME]?

Action: If yes, the interview continues. If no, ask to speak with her. If it is the wrong number, politely end the phone call and hang up.

Operator: I am calling because you do not have an updated cervical cancer screening that is performed using the Papanicolaou test. This phone call is performed in the context of a research project and your participation is voluntary. Would it be possible to speak with you for one minute about the cervical cancer screening?

Action: If yes, the interview continues (Section 1 or 2, depending on if you are a secretary or a health professional). If no, politely end the phone call and hang up.

- - - - - *Skip to **Section 1** if you are a secretary or to **Section 2** if you are a health professional* - -

Section 1 – Continue from here if you are a secretary

Operator: Can I schedule an appointment at your primary care unit [NAME OF YOUR PRIMARY CARE UNIT], to perform a Papanicolaou test, to update your cervical cancer screening program?

Action: If yes, the appointment is scheduled and the phone call is ended. Give additional information about the location of the primary care unit if this is needed. If no, politely end the phone call and hang up.

END

Section 2 – Continue from here if you are a health professional

Operator: I would like to speak with you about cervical cancer screening. Is it possible we schedule an appointment at your primary care unit [PRIMARY CARE UNIT NAME]?

Action: If yes, an appointment is scheduled and the phone call is ended. Give extra information about primary care unit location if it is needed. If not, end up the interview.

END

Appendix 2 – Health professional face-to-face interview

Health professional face-to-face interview

The following guide will be used for health professionals, to implement face-to-face appointments.

1 – Invite woman into a quiet and comfortable room, with no other patients, inside the primary care unit.

2 – Present the study protocol and invite woman to participate.

Action: If woman refuses, the interview ends. If woman accepts the interview continues and an informed consent is signed.

3 – Ask woman the motive(s) for non-adherence to cervical cancer screening.

Action: Use the table from appendix 3 to adapt the motive(s) for non-adherence to the possible motives listed. Use the arguments in the table to answer.

4 – Ask if there are any more doubts and clarify them if necessary.

5 – Ask if you could present the pamphlet of cervical cancer screening.

Action: If no, skip this step. If yes, present the document and highlight each section. Ask the woman if she would like to know more about any of the sections or has any specific doubts about them. Answer all questions and clarify any information if needed.

6 – Invite woman to be screened today (if the institution has the capability of performing the exam) or another day and define the date and time.

Action: If a woman refuses screening, thank her for all the time dispended and tell her that she can come again to talk about cervical cancer screening. If a woman accepts, screening is scheduled.

END

Appendix 3 – Potential barriers to cervical cancer screening and tools to overcome them during health professional appointments.

Barrier	Barrier description	Approach
Economic barriers	Amount needed to be paid to perform the screening.	Screening appointments and pap tests are free of charge (1).
Accessibility	Difficulties in scheduling an appointment. Location of screening is difficult to access.	Screening is performed at your primary care unit between Monday to Friday, from 8AM to 8PM.
Screening process	Previous negative experiences when undergoing the Papanicolaou test; namely pain, discomfort or constraint. Professional who performs the screening.	a) The pap test in not painful for most women. Even those who feel pain classify it only as slight. (2) b) You may ask for another medical professional to perform the pap test (female doctor if your doctor is male). c) You can bring someone from your family or a friend on the screening day.
Screening exam characteristics	Sensitivity, specificity. Perception that is not adequate/best exam.	Cervical cancer screening methods have evolved, with increased performance on detection of pre-malignant or malignant lesions. Currently, screening has the following characteristics: a) Liquid-based cytology with automatic reading of results is currently implemented and, if necessary. additional HPV tests are performed (1,3). b) Sensitivity and specificity are 76 and 89%, respectively, for this screening methodology (4).
Fear of	Fear of detecting a malignant lesion and possible need	a) High income countries which have implemented cervical cancer screening, have reduced cervical

cancer/treatment	to undergo treatment.	cancer mortality by 80% and have also reduced the occurrence of new cases of the disease (4). b) Only 6.2% of all pap tests have an abnormal result (5). c) The most common abnormal result is ASC-US (3.6% of pap tests performed) which corresponds to benign cases requiring only annual follow up (5). d) The most uncommon abnormal result is HSIL (<1% of all results). From these abnormal results, 1-4% will have an invasive carcinoma (3,5). e) Screening allows early detection of cervical cancer, more attempted treatment and better prognosis. (6)
Screening indication	Women do not perceive they are at risk, because they are too young to start screening or they do not have symptoms.	All women aged between 25 and 60 are recommended to undergo cervical cancer screening every 5 years, except if they (1): - Are being treated for cervical cancer - Are hysterectomized - Have not initiated sexual activity - Physical limitation that does not allow a pap test to be performed - Presence of signals or symptoms of gynaecologic disease (active)
Preference for private health care services	Women prefer to be screened in a private institution, e.g.: by a gynaecologist versus a family doctor	Advantages of an organized cervical cancer screening program (6): a) Higher technical skills and experience of laboratory professionals who read results and classify them b) Frequent quality control verifications c) Standardization of technical procedures

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1, lines 4-6
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 28, lines 539-542
	2b	All items from the World Health Organization Trial Registration Data Set All items available on ClinicalTrials.gov, for trial NCT03122275
Protocol version	3	Date and version identifier Page 28, line 545
Funding	4	Sources and types of financial, material, and other support Page 30, lines 574-589
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Page 1, lines 9-15 and pages 28/29, lines 547-572
	5b	Name and contact information for the trial sponsor Page 30, lines 581-584
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 30, lines 586-589

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Not applicable
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Pages 5-7, lines 84-142
	6b	Explanation for choice of comparators Page 5, lines 96-103
Objectives	7	Specific objectives or hypotheses Pages 8/9, lines 144-172
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 10, lines 192/193
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 10, lines 183-189
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 11, lines 207-218
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Pages 11-14, lines 221-281
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Not applicable

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 15, lines 283-307
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Page 10, lines 196-203 + Pages 11-14, lines 222-281
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Pages 16/17, lines 308-351
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Not applicable
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Page 18, lines 353-362

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 18, lines 358-360
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Page 18, lines 362,363
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page 19, lines 375-383
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Not applicable
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Page 19, lines 384-387

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page 20, lines 402-404
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Page 20, lines 405-414
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 20, lines 390-401 and page 21, lines 415-417
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Not applicable – DMC is considered unnecessary due to the nature of the intervention
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Not applicable
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Not applicable

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 22, lines 422-424
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 22, lines 426-432
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Page 19, lines 384-387
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 31, lines 593-598
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Page 19, lines 384-386
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Not applicable

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – Page 22, lines 436-440
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 28/29, lines 548-573
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates See attached documents: informed consent
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable No applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	7,8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	not applicable
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	not applicable
Sample size	7a	How sample size was determined	15,16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	17
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	17
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	17
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	17
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	17

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	19
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	19
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	not applicable (study is a protocol)
	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable (study is a protocol)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable (study is a protocol)
	14b	Why the trial ended or was stopped	not applicable (study is a protocol)
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable (study is a protocol)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	not applicable (study is a protocol)
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)	not applicable (study is a protocol)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable (study is a protocol)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	not applicable (study is a protocol)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable (study is a protocol)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable (study is a protocol)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable (study is a protocol)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable (study is a protocol)

Other information			
Registration	23	Registration number and name of trial registry	25
Protocol	24	Where the full trial protocol can be accessed, if available	not applicable (study is a protocol)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	27

*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.

BMJ Open

Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCAN-CC) – Automated Text Messages, Phone Calls and Face-to-face Interviews: Protocol of a population based randomized controlled trial

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Keywords:	Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

TITLE PAGE

Title: Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCAN-CC) – Automated Text Messages, Phone Calls and Face-to-face Interviews: Protocol of a population based randomized controlled trial

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ABSTRACT

Introduction

Screening is highly effective for cervical cancer prevention and control. Population based screening programs are widely implemented in high income countries, though adherence is often low. In Portugal, just over half of the women adhere to cervical cancer screening, contributing for greater mortality rates than in other European countries. The most effective adherence raising strategies are based on patient reminders, small/mass media and face-to-face educational programs, but sequential interventions targeting the general population have seldom been evaluated.

The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organized cervical cancer screening: step 1a-customized text message invitation;step 1b-customized automated phone call invitation;step 2-secretary phone call;step 3-family health professional phone call and face-to-face appointment.

Methods

A population-based randomized controlled trial will be implemented in Portuguese urban and rural areas. Women eligible for cervical cancer screening will be randomized(1:1) to intervention and control. In the intervention group, women will be invited for screening through text messages, automated phone calls, manual phone calls and health professional appointments, to be applied sequentially to participants remaining non-adherent after each step. Control will be the standard of care(written letter). The primary outcome is the proportion of women adherent to screening after step1 or sequences of steps from 1-3.

The secondary outcomes are: proportion of women screened after each step(1a,2 and 3); proportion of text messages/phone calls delivered; proportion of women previously screened in a private health institution who change to organized screening. The intervention and control groups will be compared based on intention-to-treat and per protocol analyses.

Ethics and dissemination

The study was approved by the Ethics Committee of the Northern Health Region Administration and National Data Protection Committee. Results will be disseminated through communications in scientific meetings and peer-reviewed journals.

Trial number:NCT03122275

Number of Words: 3312

Key Words

Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

STRENGTHS OF THIS STUDY

- Randomized controlled trial, using a stepwise approach, with increasing complexity and cost of interventions, to improve adherence to organized cervical cancer screening
- Interventions tested are technological and innovative
- Use of a population approach and not specific groups or minorities

LIMITATIONS OF THIS STUDY

- Contamination of interventions may occur, because randomization units are individuals and not primary care units
- Unavailability of women's mobile phone may restrict intervention delivery
- The study is restricted to women aged below 50 years, and therefore the findings may not apply to older women with limited digital literacy skills

INTRODUCTION

Cancer is one of the most important causes of morbidity and mortality, especially in developed countries.(1) A substantial part of cancer cases can be detected earlier and undergo treatment with curative intent.(2) Improvements in early detection of cancer may be achieved through increases in population awareness, enabling early consultation with health professionals, and screening programs.(2) Cervical cancer screening is one of the oldest and most effective screening programs, with relevant decreases in mortality since its implementation.(3) Although the increasing coverage of vaccination against high-risk Human Papillomavirus (HPV) strains is expected to play a major role in the prevention of cervical cancer(4), screening will still be needed, at least for non-vaccinated women and high risk groups. With the expected decrease in the number of women eligible for screening, cost reduction, including variable costs (invitation and screening), may be needed to guarantee sustainability.

Currently, in Portugal cervical cancer screening is recommended to be performed every 5 years, for women aged between 25 and 65 years old(5). Women registered at a primary care unit are invited to perform cervical cancer screening through a written letter. At a national level, just over half(5) of the invited women adhere to the cervical cancer screening and 23.5%(6) have never performed screening during life. Limited adherence to screening is expected to contribute to greater cervical cancer mortality rates in Portugal (age-standardized mortality rate: 4.9/100.000)(7), in comparison with the average in Europe's rate (27 countries, age-standardized mortality rate: 3.7/100.000)(7).

Different strategies to increase adherence to cervical cancer screening have been developed and evaluated, including interventions based on patient reminders (written letters(8–13), operator dependent phone calls(11,12,14,15) or text messages(16)), small media(17–20) (videos, brochures, pamphlets or fact sheets), mass media(21) and face-to-face educational programs(20,22).

Results from a systematic review(23), including studies conducted in high income countries, enrolling both deprived and non-deprived women, show overall increases in cervical cancer screening adherence of just over 10% with printed or phone reminders, and 4% and 8% when using small media or one-on-one education, respectively. Regarding the strategies based on the use of reminders, phone calls are more effective and cost-effective (37% uptake, costing 67$/response) than text messages (24% uptake, costing 100$/response) or written letters (19% uptake, costing 133$/response)(16). To our knowledge, no automated (machine performed) and customized phone calls have been used or compared with other methods. Additionally, text messages have been tested as cervical cancer screening reminders or invitation methods (16), but with no patient customization or built-in mechanisms for reply to the messages. This method was tested as appointment reminders in hospitals (24) and primary health care health services(25), with 10% increases in adherence to scheduled appointments, but also as part of obesity control programs(26). Some of these programs allow for patient interaction, enabling them to make a data input on their health status or simply reply after receiving the intervention(26). This bi-directional approach, could be used for cancer screening invitation and appointment scheduling, by allowing the invited people to confirm their interest to be screened, using a text message or a reply to an automatic phone call. A recent systematic review on the use of automated telephone communication systems highlighted the effectiveness of unidirectional/bi-directional phone-delivered interventions on the uptake increase of screening programs(27).

Educational programs aiming to increase adherence to cervical cancer screening have been implemented using face-to-face interventions with trained professionals(20,22), sometimes using support videos or pamphlets(20) or delivered through motivational phone call(28). These programs are highly tailored to each patient, and therefore difficult to implement at a population level, because these are resource-intensive activities. In a population-based approach, a multistage intervention is needed, implementing first, cheaper and easier to use

interventions such as text messages and automated phone calls. Women refractory to these strategies should receive more expensive and patient tailored interventions such as phone calls performed by trained professionals as reminders or face-to-face appointments to provide information on cervical cancer screening. Most of the interventions described in the literature target only deprived populations(8,15,18) or from an ethnic group/social minorities(15,18,19,29) and only a few cases use multistage approaches, where different interventions (written letter invitation, written letter reminder, phone call reminder) were sequentially applied till women adhere to screening(8).

Objectives

The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organized cervical cancer screening, in relation with the standard of care (invitation by written letter), implemented through three steps:

Step 1a – customized text message invitation;

Step 1b – customized automated phone call invitation;

Step 2 – secretary phone call;

Step 3 – health professional phone call and face-to-face appointment.

As primary objectives, we intend to test the superiority of the intervention based on step 1 (1a+1b), and multistage interventions based on steps 1 and 2, and steps 1 to 3.

The secondary objectives will be the following:

1. To test the non-inferiority of interventions based on step 1a and step 1 (1a+1b), considering a non-inferiority limit of 5%;
2. To test the superiority of the specific components of the multistage intervention corresponding to step 2 and step 3;
3. To quantify the differences in adherence to cervical cancer screening, for the intervention based on step 1 (1a+1b) and multistage interventions based on steps 1 and 2, and steps 1 to 3, between: a) Urban and rural areas; b) Younger and older populations; c) Deprived and non-deprived populations; d) Never vs. ever users of organized screening; e) History of regular vs. irregular participation in organized screening programs.

4. To quantify the differences in adherence to cervical cancer screening when using a positive or a neutral content of text messages and automated phone calls, in step 1.
5. To estimate the proportion of women who were undergoing performing cervical cancer screening in private health care services who started to be screened in an organized cervical cancer screening program, after a health professional face-to-face appointment at their primary care unit.

Intention-to-treat analysis will be used as primary strategy for all comparisons between interventions and control. Secondary per-protocol analysis will also be conducted.

The current interventions intend to be inexpensive and easy to implement so they can be used both in high and low-income countries, at a population level, as strategies to increase the adherence to cervical cancer screening.

METHODS AND ANALYSIS

Setting

The study will be conducted among women with a medical registration at two primary health care areas in the north of mainland Portugal, namely *Porto Ocidental*, serving densely populated urban areas near the coast, and *Marão e Douro Norte*, located inland, covering scarcely populated and predominantly rural areas. These were selected because they have low adherence to cervical cancer screening: 32% for *Porto Ocidental* and 61% for *Marão e Douro Norte*).(30)

Design

This investigation is based on a population-based randomized controlled trial, with a parallel design, as depicted in Figure 1.

Women eligible for cervical cancer screening will be randomized 1:1 within each primary health care unit.

The intervention will comprise invitation to screening, through the following sequential steps:

Step 1 – Automated text messages (step 1a)/automated phone calls (step 1b);

Step 2 – Manual phone calls performed by secretaries, implemented one to two months after step 1, among women remaining non-adherent one month after step 1;

Step 3 – Health professional phone call and appointments, implemented one to two months after step 2, among women remaining non-adherent one month after step 2.

Intervention stops whenever the participants adhere to organized screening or after undergoing the whole intervention. Control will be the standard of care (invitation by written letter).

---------- INSERT FIGURE 1 HERE ----------

Participants

Inclusion criteria:

a) Women aged between 25 and 49 years, and eligible for cervical cancer screening (having started sexual activity, not hysterectomized, not undergoing cervical cancer treatment);

b) Medical registration at any of the primary health care units selected for this study.

Although cervical cancer screening programs are recommended for women with ages till 65 years, will only be considered for this study those younger than 50 years, who are expected to have higher levels of digital literacy, and therefore more likely to benefit from this type of intervention. Nevertheless, this may limit the possibility of generalising our findings to older women who are less proficient in the use of mobile technology.

Exclusion criteria:

No mobile phone number available at the National Health Service database.

Intervention

The intervention comprises different strategies for invitation to cervical cancer screening, to be applied sequentially, in three steps.

Step 1 (1a + 1b) – Automated text messages/phone calls

Women randomized to the intervention arm will be assigned a date and hour for screening by the primary health care unit secretaries, who will then upload the women's phone number, first and last name, name of the primary care unit and appointment date/hour in the software selected for implementation of step 1: File2Mail v.2.2, Smart IVR v.1.1, Smart Message v.3.1 and Speech2Go v.1.1. Personalized text messages (Step 1a), with a maximum length of 320 characters, and phone calls (Step 1b), with a maximum duration of 30 seconds, will then be automatically assembled and sent to the study participants.

When a screening invitation is accepted, either in step 1a or step 1b, a text message reminder will be sent to women 24-48h before the appointment (Figure 2 – reminder message).(25)

Step 1a – Automated text messages

Two models of invitation text message will be randomized 1:1 within each primary health care unit (Figure 2); invitation message 1 has a neutral style (close to the usual written invitation letter) and invitation message 2 has a gain-frame and positive style of writing.(31) The content validity of the invitation messages was tested among a few potentially eligible women, and modifications were implemented, namely the name of the primary care unit and information stating that the appointment has no co-payments was added to the original text message.

Women are asked to confirm their interest to undergo cervical cancer screening at the proposed date and time, answering the invitation with a text message saying "CONFIRM". If they do not confirm within 24 hours, they will additionally receive an automated phone call (step 1b).

Step 1b – Automated phone calls

A phone call invitation will be performed in after-hours period (17-20h), using a humanized female voice, and follows the same structure of the text messages (Figure 2 and Figure 3 –

invitation phone call 1 and 2). Women will receive phone call 1 if they do not answer the invitation message 1 and receive phone call 2 if they did not answer the invitation message 2.

Women are asked to press the number 1 for appointment confirmation or the number 2 if they want to receive a phone call from the primary care unit secretary. The audio message will be repeated three times in the same call, or until women provide the feed-back required.

If women do not answer the phone call or do not press the number 1 or 2, a new automated phone call will be scheduled for the next day, for a maximum of three days (Figure 3).

---------- INSERT FIGURE 2 HERE ---------- ----------

---------- INSERT FIGURE 3 HERE ---------- ----------

Step 2 – Secretary phone call

Women who do not confirm the appointment in step 1 or do not attend organized cervical cancer screening are enrolled in step 2. This comprises an invitation phone call performed in after-hours period (17-20h), by the secretary of the corresponding primary care unit. Secretaries will be trained by the research team and will follow a predefined script (Appendix 1). If women do not answer the call, it will be repeated daily, for a maximum of three days. A date and hour for cervical cancer screening will be scheduled for women who agree to participate.

Step 3 – Health professional phone call and face-to-face appointment

Women who do not answer the phone during step 2, or do not participate in organized cervical cancer screening after the scheduled appointment, will be enrolled in step 3. This comprises a phone call and a face-to-face appointment performed by a health professional from the primary care unit (family nurses or resident medical doctors), specifically trained for this step of the intervention. Phone calls will be performed in after-hours period (17-20h), aiming to schedule an appointment, using a predefined script (Appendix 2). If women do not answer the call, it will be repeated daily, for a maximum of three days. During appointments, screening will be described and doubts clarified using the standard North Portugal cervical cancer screening pamphlet. Health professional will identify possible barriers felt by women and will try to overcome them using predefined arguments (Appendix 3). Additionally, women who agree to participate will be screened after the interview or scheduled for another date, defined according to their and the Service's convenience.

Outcomes

The primary outcome is defined as follows:

Adherence to cervical cancer screening

Proportion or cumulative proportion of women who performed cervical cancer screening on the scheduled date, among those who were invited, after step 1 or sequences of steps from 1 to 3, as applicable.

The secondary outcomes are defined as follows:

Adherence to cervical cancer screening (steps 1a, 2 and 3)

Proportion of women who performed cervical cancer screening on the scheduled date, among those who were invited, after step 1a, after step 2 or after step 3.

Text message status

Proportion of text messages received with confirmation, from those that were sent.

Automated phone call status

Proportion of automated phone calls delivered, from those that were attempted.

Change from opportunistic to organized screening

Proportion of women undergoing opportunistic cervical cancer screening in a private health institution who change to organized cervical cancer screening.

The index dates for adherence assessment will be the following: 1) the day after the appointment date, for text message invitation, secretary phone calls and written letters; 2) two months after the intervention based on face-to-face interviews conducted by health professionals.

Sample Size

Sample size was estimated considering the use of two-sided tests, for a significance level of 5% and a statistical power of 90%, intending the comparison of intervention and control groups regarding the outcomes defined as part of the primary objective.

Step 1 (1a+1b)

We estimate an adherence to screening based on invitation through a written letter of 40% (based on SiiMA Rastreios *software:* Portuguese software for cancer screening), and we intend to detect an increase to 50% with the intervention based on step 1. We expect this 10% increase because two different techniques of invitation will be used (text message and automated phone call) and an electronic reminder will be sent 24h prior to the appointment.(23) The minimum sample size determined for each group is 519 women.

Steps 1 and 2

We expect a 45% cumulative adherence proportion in the control group, after the interventions based on steps 1 and 2; an increase in relation to the expected adherence in the control group after steps 1, from 40 to 45%, may be anticipated because for step 2 there will be a longer period between baseline and outcome assessment. We expect a cumulative adherence proportion of 60% in the intervention group, which is a conservative estimate, considering the published effectiveness of phone calls.(11,12) The minimum sample size determined for each group is 244 women.

Steps 1 to 3

We expect 50% and 70% cumulative adherence proportion in the control and intervention groups, respectively after the interventions based on steps 1 to 3. In the control group, an

increase in comparison to the expected adherence after steps 2, from 45 to 50%, may be anticipated due to the longer period between baseline and outcome assessment. The magnitude of increase in adherence in the intervention group, was estimated based on the previously observed effectiveness of face-to-face appointments in other settings.(20). The minimum sample size determined for each group is 134 women.

The overall sample size needed is 1038 (519*2), determined by step 1 interventions, since the remaining primary outcomes require a smaller sample size. Nevertheless, a 10% greater number of participants will be recruited to account for the potential withdrawal of one health care unit before the completion of the stepwise intervention. We anticipate that the drop-out of individual participants will be lower than 1%, during the steps 2 and 3 of the intervention; this low value is expected because we will use an opt-out strategy, so that only women who actively express their willingness for not receiving further interventions are considered as drop-outs.

The statistical analysis for accomplishment of secondary objectives are exploratory and therefore the sample size was not determined to consider them. Nevertheless, the sample size defined for the study, is expected to have enough power to test the superiority of the isolate effect of step 1b, step 2 or step 3. Additionally, the sample size is also enough to test non-inferiority secondary objectives, assuming one-sided tests, a significance level of 2.5%, power of 90%, an adherence proportion in control group of 40% and 50% in experimental group and a non-inferiority limit of 5%.

Randomization

Women will be randomized 1:1 into the intervention or control groups (Figure 1). A woman randomized to the intervention or control will belong to that study arm until the end of the study. Primary care units will extract a list of eligible women for screening, fulfilling study criteria, from SiiMA Rastreios *software* (national software for cancer screening eligibility). Principal investigator will generate the randomization sequence through Excel v.Office 365. All women registered and fulfilling eligibility criteria will be assigned to intervention or control by the primary care unit secretaries. If a woman is randomized to the intervention group, she will be randomized again to receive a neutral or a positively framed invitation text message/automated phone call on a 1:1 ratio (Figure 3). There will be no blinding of the participants, health professionals or elements of the research team.

Contamination is possible, especially because screening can be obtained for free in both groups and women exposed to interventions may live geographically near women belonging to control group. Therefore, the participation of women from the intervention arm may influence the adherence of women in the control group. Contamination will dilute the effect of the interventions to be tested, and all the effectiveness estimates computed will be conservative. Although we cannot accurately predict the extent of the contamination, we may speculate that it will increase with the complexity of the interventions, being higher for step 3 than for step 1. Zip-code randomization would contribute to minimize contamination, but it would not be feasible due to the unavailability of complete zip-codes on SiiMA Rastreios. We did not opt for randomization of primary care units because the number of randomization units available is low.

Data collection

Information about adherence to cervical cancer screening after interventions or standard of care (invitation letter) will be obtained using the national software for cancer screening eligibility – SiiMA Rastreios. This platform will also be used to collect data about women's previous participation in cervical cancer screening.

Patient appointment confirmation obtained from text messages and phone calls will be saved directly by the software into the study laptop database.

Sociodemographic characteristics, including age, education level, parity, marital and employment status and type of job will be manually extracted from the electronic medical record (EMR). Age and parity will be collected as continuous variables and all the others as categorical. Education level will comprise the categories lower than 9 years of education, 9 to 11 years, 12 or more years. Marital status will be coded as single, married or divorced. Employment status will be defined as student, employed, unemployed or retired and the occupation as upper white collar, lower white collar, high skilled blue collar and low skilled blue collar.

All the information written in the database will be pseudo-anonymized, using a unique identifier and only the principal investigator will have the encryption key. Only members of the research team will have access to the database. All medical data will be collected from EMR by medical doctors belonging to the research team.

Statistical analysis

Intention-to-treat analysis will be used as the primary strategy for all comparisons between interventions and control. Two secondary per-protocol analyses will also be conducted, considering only the following subsets of participants:

a) women who receive the invitation

- experimental arm: women who receive a text message/phone call, as confirmed by the software used for automated delivery of the intervention

- control arm: women who received a written letter, *i.e.* no invitation letter returned

b) women who have an appointment scheduled:

- experimental arm: women who confirm the appointment by replying to the text message or automatic phone call invitation

- control arm: women assumed to have received the invitation letter with the appointment scheduled, *i.e.* letter not returned.

Adherence proportions will be determined for step 1a, step 1b, step 1a+1b, step 2, step 3, and sequences of steps from 1 to 3. Differences of adherence proportions between the intervention and control groups will be tested using chi-squared test or Fisher exact test as appropriate. Binary logistic regression may be used to control for confounding, or in secondary analyses of the isolate effects of steps 1b, 2 and 3. Adherence to screening will be considered as the dependent variable. Independent variables will include study arm and potential confounders selected among age, education, marital status, number of children, employment status, type of living area (rural vs. urban), previous adherence to cervical cancer screening and deprivation index.

Additionally, a stratified analysis will be performed, using as strata variables age (high vs. low), rurality (rural vs. urban), deprivation (deprived vs. non-deprived), regularity of previous participation (regular vs. irregular participation) and previous participation (ever vs. never participation).

Missing data is expected to be low for all the variables obtained from medical records, because they are collected on a regular basis by all general practitioners during appointments, using a structured entry form. No imputation of missing data is being planned.

All tests are two-tailed, with a p-value of 0.05 indicating statistical significance for superiority objectives or one-tailed with a p-value of 0.025 for non-inferiority objectives.

Ethics and dissemination

This study was approved by Portuguese regional ethics committee – *Comissão de Ética da Administração Regional de Saúde do Norte* (number: 20/2017) and by National Data Protection Committee (number: 11467/2016). The trial was registered and assigned the number NCT03122275.

For step 1 interventions (automated text messages/phone calls) obtaining an informed consent is not feasible, however, we consider that the benefits for participants and society outweigh the ethical aspects raised and the ethics committee recognized it. Women participating or not will not influence access and type of health care provided.

In steps 2 and 3, the secretaries or health professionals will explain the study and obtain verbal informed consent during the phone calls. In step 3, the health professionals will obtain written informed consent from all participants undergoing this step of the intervention.

All the software used to perform automated text messages and phone calls follow the Health Insurance Portability and Accountability Act (HIPAA) protocol and article number 8 of the European Convention of Human Rights.

A manuscript addressing the primary objective of this trial will be submitted for publication in a peer-reviewed journal. Additional manuscripts will be submitted for publication, intending to answer the secondary objectives. Communications in national and international scientific meetings are also expected. Technical reports will be made available to the primary care units and institutions involved in this study.

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OTHER INFORMATION

Trial registration

Trial identifier: NCT03122275 (registered on Clinical Trials.gov)

Registry name: Stepwise Strategy to Improve CANcer Screening Adherence: Cervical Cancer (SCAN-CC)

Protocol version

11 April 2017. 1st protocol version

Roles and responsibilities

All the authors of the manuscript follow the four criteria of authorship defined by ICMJE.

A description of responsibilities/author can be found below:

João Firmino-Machado

Protocol responsibilities: Conceptual design of the research project, drafted the first version of the protocol manuscript and final manuscript production.

Study implementation responsibilities: Responsible for study presentation and enrolment of all primary care units, intervention implementation, data collection and analysis, and manuscript writing.

Romeu Mendes

Protocol responsibilities: Conceptual design of the research project and critical review of the manuscript.

Study implementation responsibilities: Responsible for study presentation and enrolment of the primary care units from ACeS Marão e Douro Norte, intervention implementation and data collection.

Amélia Moreira

Protocol responsibilities: Conceptual design of the research project and critical review of all protocol drafts.

Study implementation responsibilities: Responsible for study presentation and enrolment of the primary care units from ACeS Porto Oriental, intervention implementation.

Nuno Lunet

Protocol responsibilities: Conceptual design of the research project and critical review of all versions of the manuscript.

Study implementation responsibilities: Responsible for the supervision of the study implementation, data collection and analysis, and writing of the manuscripts.

All the authors gave a final approval of the version to be published and agreed to be accountable for all aspects of the work.

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This is an academic trial that is supported both by the academic and the primary care institutions involved. Although the members of the research team belong to these institutions, the latter will not interfere in data analysis, results interpretation and decision to submit the manuscripts for publication.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no organisation influenced the authors about the decision to submit for publication the current work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

Transparency declaration:

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been registered.

Figures

Legend: † - outcome assessment

Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.

Figure 2 – Content for text messages and phone calls.

Figure 3 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

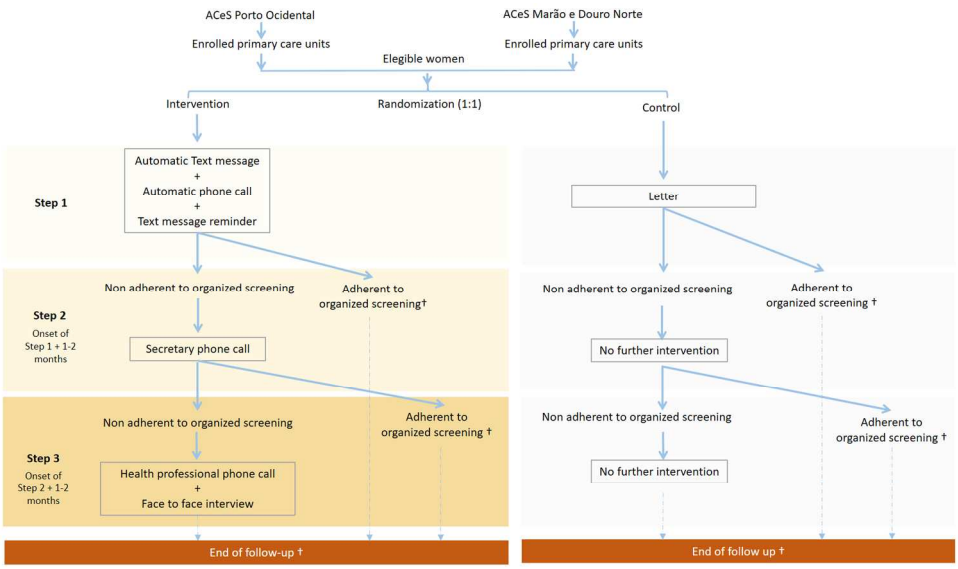

Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.
Legend: † - outcome assessment

402x231mm (300 x 300 DPI)

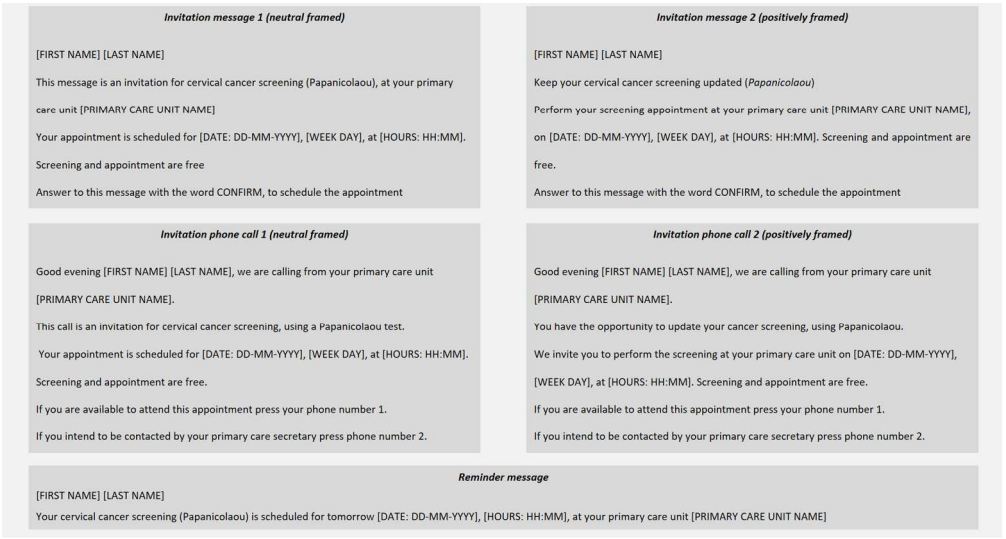

Figure 2 – Content for text messages and phone calls.

162x86mm (300 x 300 DPI)

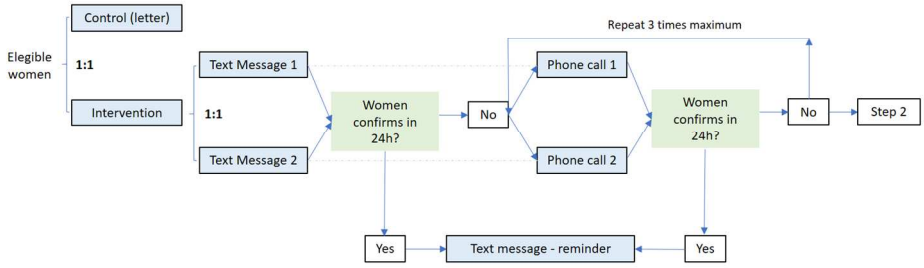

Figure 3 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

359x135mm (300 x 300 DPI)

Appendix 1 – Secretary and health professional phone call protocol

Secretary and health professional phone call structure

Follow this interview model when calling women enrolled in the current research study.

Operator: Good evening, my name is [SECRETARY OR HEALTH PROFESSIONAL NAME]. I am calling from [PRIMARY HEALTH CARE CENTER NAME]. Am I speaking with [WOMAN´S NAME]?

Action: If yes, the interview continues. If no, ask to speak with her. If it is the wrong number, politely end the phone call and hang up.

Operator: I am calling because you do not have an updated cervical cancer screening that is performed using the Papanicolaou test. This phone call is performed in the context of a research project and your participation is voluntary. Would it be possible to speak with you for one minute about the cervical cancer screening?

Action: If yes, the interview continues (Section 1 or 2, depending on if you are a secretary or a health professional). If no, politely end the phone call and hang up.

- - - - - *Skip to **Section 1** if you are a secretary or to **Section 2** if you are a health professional* - -

Section 1 – Continue from here if you are a secretary

Operator: Can I schedule an appointment at your primary care unit [NAME OF YOUR PRIMARY CARE UNIT], to perform a Papanicolaou test, to update your cervical cancer screening program?

Action: If yes, the appointment is scheduled and the phone call is ended. Give additional information about the location of the primary care unit if this is needed. If no, politely end the phone call and hang up.

END

Section 2 – Continue from here if you are a health professional

Operator: I would like to speak with you about cervical cancer screening. Is it possible we schedule an appointment at your primary care unit [PRIMARY CARE UNIT NAME]?

Action: If yes, an appointment is scheduled and the phone call is ended. Give extra information about primary care unit location if it is needed. If not, end up the interview.

END

Appendix 2 – Health professional face-to-face interview

Health professional face-to-face interview

The following guide will be used for health professionals, to implement face-to-face appointments.

1 – Invite woman into a quiet and comfortable room, with no other patients, inside the primary care unit.

2 – Present the study protocol and invite woman to participate.

Action: If woman refuses, the interview ends. If woman accepts the interview continues and an informed consent is signed.

3 – Ask woman the motive(s) for non-adherence to cervical cancer screening.

Action: Use the table from appendix 3 to adapt the motive(s) for non-adherence to the possible motives listed. Use the arguments in the table to answer.

4 – Ask if there are any more doubts and clarify them if necessary.

5 – Ask if you could present the pamphlet of cervical cancer screening.

Action: If no, skip this step. If yes, present the document and highlight each section. Ask the woman if she would like to know more about any of the sections or has any specific doubts about them. Answer all questions and clarify any information if needed.

6 – Invite woman to be screened today (if the institution has the capability of performing the exam) or another day and define the date and time.

Action: If a woman refuses screening, thank her for all the time dispended and tell her that she can come again to talk about cervical cancer screening. If a woman accepts, screening is scheduled.

END

Appendix 3 – Potential barriers to cervical cancer screening and tools to overcome them during health professional appointments.

Barrier	Barrier description	Approach
Economic barriers	Amount needed to be paid to perform the screening.	Screening appointments and pap tests are free of charge (1).
Accessibility	Difficulties in scheduling an appointment. Location of screening is difficult to access.	Screening is performed at your primary care unit between Monday to Friday, from 8AM to 8PM.
Screening process	Previous negative experiences when undergoing the Papanicolaou test; namely pain, discomfort or constraint. Professional who performs the screening.	a) The pap test in not painful for most women. Even those who feel pain classify it only as slight. (2) b) You may ask for another medical professional to perform the pap test (female doctor if your doctor is male). c) You can bring someone from your family or a friend on the screening day.
Screening exam characteristics	Sensitivity, specificity. Perception that is not adequate/best exam.	Cervical cancer screening methods have evolved, with increased performance on detection of pre-malignant or malignant lesions. Currently, screening has the following characteristics: a) Liquid-based cytology with automatic reading of results is currently implemented and, if necessary. additional HPV tests are performed (1,3). b) Sensitivity and specificity are 76 and 89%, respectively, for this screening methodology (4).
Fear of	Fear of detecting a malignant lesion and possible need	a) High income countries which have implemented cervical cancer screening, have reduced cervical

cancer/treatment	to undergo treatment.	cancer mortality by 80% and have also reduced the occurrence of new cases of the disease (4). b) Only 6.2% of all pap tests have an abnormal result (5). c) The most common abnormal result is ASC-US (3.6% of pap tests performed) which corresponds to benign cases requiring only annual follow up (5). d) The most uncommon abnormal result is HSIL (<1% of all results). From these abnormal results, 1-4% will have an invasive carcinoma (3,5). e) Screening allows early detection of cervical cancer, more attempted treatment and better prognosis. (6)
Screening indication	Women do not perceive they are at risk, because they are too young to start screening or they do not have symptoms.	All women aged between 25 and 60 are recommended to undergo cervical cancer screening every 5 years, except if they (1): - Are being treated for cervical cancer - Are hysterectomized - Have not initiated sexual activity - Physical limitation that does not allow a pap test to be performed - Presence of signals or symptoms of gynaecologic disease (active)
Preference for private health care services	Women prefer to be screened in a private institution, e.g.: by a gynaecologist versus a family doctor	Advantages of an organized cervical cancer screening program (6): a) Higher technical skills and experience of laboratory professionals who read results and classify them b) Frequent quality control verifications c) Standardization of technical procedures

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1, lines 4-6
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 28, lines 539-542
	2b	All items from the World Health Organization Trial Registration Data Set All items available on ClinicalTrials.gov, for trial NCT03122275
Protocol version	3	Date and version identifier Page 28, line 545
Funding	4	Sources and types of financial, material, and other support Page 30, lines 574-589
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Page 1, lines 9-15 and pages 28/29, lines 547-572
	5b	Name and contact information for the trial sponsor Page 30, lines 581-584
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 30, lines 586-589

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Not applicable
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Pages 5-7, lines 84-142
	6b	Explanation for choice of comparators Page 5, lines 96-103
Objectives	7	Specific objectives or hypotheses Pages 8/9, lines 144-172
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 10, lines 192/193
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 10, lines 183-189
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 11, lines 207-218
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Pages 11-14, lines 221-281
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Not applicable

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 15, lines 283-307
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Page 10, lines 196-203 + Pages 11-14, lines 222-281
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Pages 16/17, lines 308-351
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Not applicable
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Page 18, lines 353-362

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 18, lines 358-360
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Page 18, lines 362,363
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page 19, lines 375-383
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Not applicable
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Page 19, lines 384-387

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page 20, lines 402-404
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Page 20, lines 405-414
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 20, lines 390-401 and page 21, lines 415-417
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Not applicable – DMC is considered unnecessary due to the nature of the intervention
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Not applicable
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Not applicable

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 22, lines 422-424
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 22, lines 426-432
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Page 19, lines 384-387
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 31, lines 593-598
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Page 19, lines 384-386
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Not applicable

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – Page 22, lines 436-440
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 28/29, lines 548-573
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates See attached documents: informed consent
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable No applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	7,8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	not applicable
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	not applicable
Sample size	7a	How sample size was determined	15,16
	7b	When applicable, explanation of any interim analyses and stopping guidelines	not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	17
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	17
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	17
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	17
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	17

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	19
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	19
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	not applicable (study is a protocol)
	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable (study is a protocol)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable (study is a protocol)
	14b	Why the trial ended or was stopped	not applicable (study is a protocol)
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable (study is a protocol)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	not applicable (study is a protocol)
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)	not applicable (study is a protocol)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable (study is a protocol)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	not applicable (study is a protocol)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable (study is a protocol)
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable (study is a protocol)
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable (study is a protocol)
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable (study is a protocol)

Other information			
Registration	23	Registration number and name of trial registry	25
Protocol	24	Where the full trial protocol can be accessed, if available	not applicable (study is a protocol)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	27

*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.