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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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**28 ABSTRACT****29 Introduction**

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

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

**41 Methods**

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

50

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

56 **Ethics and dissemination**

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

61 **Trial registration number**

62 NCT03122275

66 **Number of Words:** 3312

68 **Key Words**

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

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2  
3 73 **STRENGTHS OF THIS STUDY**  
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- 5  
6 74 - Randomized controlled trial, using a stepwise approach, with increasing complexity  
7  
8 75 and cost of interventions, to improve adherence to organized cervical cancer screening  
9  
10 76 - Interventions tested are technological and innovative  
11  
12 77 - Use of a population approach and not specific groups or minorities  
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17  
18 79 **LIMITATIONS OF THIS STUDY**  
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- 20  
21 80 - Contamination of interventions may occur, because randomization units are  
22  
23 81 individuals and not primary care units  
24  
25 82 - Unavailability of women's mobile phone may restrict intervention delivery  
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84 INTRODUCTION

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

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

102 Results from a systematic review(20) show overall increases in cervical cancer screening  
103 adherence of just over 10% with printed or phone reminders, and 4% and 8% when using small  
104 media or one-on-one education, respectively. Regarding the strategies based on the use of  
105 reminders, phone calls are more effective and cost-effective (37% uptake, costing  
106 67\$/response) than text messages (24% uptake, costing 100\$/response) or written letters  
107 (19% uptake, costing 133\$/response).(13) To our knowledge, no automated (machine  
108 performed) and customized phone calls have been used or compared with other methods.

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

114 Educational programs aiming to increase adherence to cervical cancer screening have been  
115 implemented using face-to-face interventions with trained professionals(17,19), sometimes  
116 using support videos or pamphlets(17). These programs are highly tailored to each patient, and  
117 therefore difficult to implement at a population level, because these are resource-intensive  
118 activities. In a population-based approach, a multistage intervention is needed, implementing  
119 first, cheaper and easier to use interventions such as text messages and automated phone  
120 calls. Women's refractory to these strategies should receive more expensive and patient  
121 tailored interventions such as phone calls performed by trained professionals as reminders or  
122 face-to-face appointments to provide information on cervical cancer screening. Most of the  
123 interventions described in the literature target only deprived populations(5,12,15) or from an  
124 ethnic group/social minorities(12,15,16,24) and only a few cases use multistage approaches  
125 (8,15).

126



127 **Objectives**

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

131 Step 1a – customized text message invitation;

132 Step 1b – customized automated phone call invitation;

133 Step 2 – secretary phone call;

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

135

136 As primary objectives, we intend to test the superiority of the intervention based on step 1  
137 (1a+1b), and multistage interventions based on steps 1 and 2, and steps 1 to 3.

138

139 The secondary objectives will be the following:

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

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3 150 4. To quantify the differences in adherence to cervical cancer screening when using a  
4  
5 151 positive or a neutral content of text messages and automated phone calls, in step 1.  
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7 152 5. To estimate the proportion of women who were undergoing performing cervical  
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9 153 cancer screening in private health care services who started to be screened in an  
10  
11 154 organized cervical cancer screening program, after a health professional face-to-face  
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13 155 appointment at their primary care unit.  
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19 157 Intention-to-treat analysis will be used as primary strategy for all comparisons between  
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21 158 interventions and control. Secondary per-protocol analysis will also be conducted.  
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161 **METHODS AND ANALYSIS**

162 **Setting**

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

169 **Design**

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

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

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

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

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

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

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

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

184

## 185 **Participants**

### 186 Inclusion criteria:

- 187 a) Women aged between 25 and 49 years, and eligible for cervical cancer screening  
188 (having started sexual activity, not hysterectomized, not undergoing cervical cancer  
189 treatment);  
190 b) Medical registration at any of the primary health care units selected for this study;

### 191 Exclusion criteria:

192 No mobile phone number available at the National Health Service database.  
193

194

## 195 **Intervention**

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

198

199

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

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

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

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

211 Step 1a – Automated text messages

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

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

222 Step 1b – Automated phone calls

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

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

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

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

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

234

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235 Step 2 – Secretary phone call

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

243

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

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

257

258 **Outcomes**

259 The primary outcome is defined as follows:

260 Adherence to cervical cancer screening

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

265 The secondary outcomes are defined as follows:

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

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

270 Text message status

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

273 Automated phone call status

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

276 Change from opportunistic to organized screening

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

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



283 **Sample Size**

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

288 Step 1 (1a+1b)

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

296 Steps 1 and 2

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

304 Steps 1 to 3

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

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

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

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

319

320 **Randomization**

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

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

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

338

339 **Data collection**

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

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

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

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

352

353 **Statistical analysis**

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

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

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

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

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

377

## 378 Ethics and dissemination

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

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

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

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

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

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**REFERENCES**

1. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388: 1459–1544.

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

3. IARC. Cervical Cancer and Screening. In: IARC Handbook of Cancer Prevention, vol.10, Chapter 1. 2005.

4. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial. *Lancet* 2004;364: 1757–65.

5. Lantz PM, Stencil D, Lippert MT, Beversdorf S, Jaros L, Remington PL. Breast and cervical cancer screening in a low-income managed care sample: The efficacy of physician letters and phone calls. *Am J Public Health* 1995;85: 834–6.

6. Buehler SK, Parsons WL. Effectiveness of a call/recall system in improving compliance with cervical cancer screening: A randomized controlled trial. *Cmaj* 1997;157: 521–6.

7. Morrell S, Taylor R, Zeckendorf S, Niciak A, Wain G, Ross J. How much does a reminder letter increase cervical screening among under-screened women in NSW? *Aust N Z J Public Health* 2005;29: 78–84.

8. Eaker S, Adami H, Granath F, Wilander E. A Large Population-Based Randomized

- 1  
2  
3 421 Controlled Trial to Increase Attendance at Screening for Cervical Cancer. *Cancer*  
4  
5 422 *Epidemiol Biomarkers Prev* 2004;13: 346–55.  
6  
7  
8  
9 423 9. TM V, Glass A, RE G, PA LC, Lichtenstein E. The safety net: a cost-effective  
10  
11 424 approach to improving breast and cervical cancer screening. *J Women's Heal*  
12  
13 425 2003;12: 789–798.  
14  
15  
16 426 10. Jensen H, Svanholm H, Stovring H, Bro F. A primary healthcare-based  
17  
18 427 intervention to improve a Danish cervical cancer screening programme: a cluster  
19  
20 428 randomised controlled trial. *J Epidemiol Community Heal* 2009;63: 510–5.  
21  
22  
23  
24 429 11. Broberg G, Jonasson JM, Ellis J, Gyrd-Hansen D, Anjemark B, Glantz A, et al.  
25  
26 430 Increasing participation in cervical cancer screening: Telephone contact with  
27  
28 431 long-term non-attendees in Sweden. Results from RACOMIP, a randomized  
29  
30 432 controlled trial. *Int J Cancer* 2013;133:164–71.  
31  
32  
33  
34 433 12. Women L, Randomized A, Trial C, Dietrich AJ, Tobin JN, Cassells A, et al.  
35  
36 434 Telephone Care Management To Improve Cancer Screening among low-income  
37  
38 435 women. *Ann Intern Med.* 2006;144: 563–71.  
39  
40  
41 436 13. Marhayu R, Rashid A, Ramli S, John J. Cost Effective Analysis of Recall Methods  
42  
43 437 for Cervical Cancer Screening in Selangor - Results from a Prospective  
44  
45 438 Randomized Controlled Trial. *Asian Pac J Cancer Prev* 2014;15: 1–5.  
46  
47  
48  
49 439 14. Byles JE, Redman S, Sanson-fisher RW, Boyle CA. Effectiveness of two direct-mail  
50  
51 440 strategies to encourage women to have cervical (Pap) smears. *Health Promot*  
52  
53 441 *Int.* 1995;10: 5–16.  
54  
55  
56  
57 442 15. Rimer BK, Conaway M, Lyna P, Glassman B, Yarnall KSH, Lipkus I, et al. The  
58  
59  
60



443 impact of tailored interventions on a community health center population.

444 Patient Educ Couns 1999;37: 125–40.

445 16. Taylor VM. A Randomized Controlled Trial of Interventions to Promote Cervical

446 Cancer Screening Among Chinese Women in North America. CancerSpectrum

447 Knowl Environ 2002;94: 670–7.

448 17. McAvoy BR, Raza R. Can health education increase uptake of cervical smear

449 testing among Asian women? BMJ 1991;302: 833–6.

450 18. Howe A, Owen-Smith V, Richardson J. The impact of a television soap opera on

451 the NHS Cervical Screening Programme in the North West of England. J Public

452 Health Med 2002;24:299–304.

453 19. Valanis BG, Glasgow RE, Mullooly J, Vogt TM, Whitlock EP, Boles SM, et al.

454 Screening HMO women overdue for both mammograms and pap tests. Prev

455 Med 2002;34: 40–50.

456 20. Baron RC, Rimer BK, Breslow RA, Coates RJ, Kerner J, Melillo S, et al. Client-

457 Directed Interventions to Increase Community Demand for Breast, Cervical, and

458 Colorectal Cancer Screening - A systematic review. Am J Prev Med 2008;35: 34-

459 55.

460 21. Arora S, Burner E, Terp S, Nok Lam C, Nercisian A, Bhatt V, et al. Improving

461 attendance at post-emergency department follow-up via automated text

462 message appointment reminders: A randomized controlled trial. Acad Emerg

463 Med 2015;22: 31–7.

464 22. Leong KC, Chen WS, Leong KW, Mastura I, Mimi O, Sheikh MA, et al. The use of

- 1  
2  
3 465 text messaging to improve attendance in primary care: a randomized controlled  
4  
5 466 trial. Fam Pract 2006;23: 699–705.  
6  
7  
8  
9 467 23. Riley WT, Rivera DE, Atienza AA, Nilsen W, Allison SM, Mermelstein R. Health  
10  
11 468 behavior models in the age of mobile interventions: Are our theories up to the  
12  
13 469 task? Transl Behav Med 2011;1: 53–71.  
14  
15  
16 470 24. Project F, Paskett ED, Tatum CM, Agostino RD, Rushing J, Velez R, et al.  
17  
18 471 Community-based Interventions to Improve Breast and Cervical Cancer  
19  
20  
21 472 Screening : Results of the Forsyth County Cancer Screening 1999;8: 453–9.  
22  
23  
24 473 25. Direct Extraction from SIARS software, on 20/09/2016, at 14:00h.  
25  
26  
27 474 26. Rothman AJ, Bartels RD, Wlaschin J, Salovey P. The strategic use of gain- and  
28  
29 475 loss-framed messages to promote healthy behavior: How theory can inform  
30  
31 476 practice. J Commun 2006;56: 202–20.  
32  
33  
34 477  
35  
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480     **OTHER INFORMATION**

481     **Trial registration**

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

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

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485

486     **Protocol version**

487     11 April 2017. 1st protocol version

488

489     **Roles and responsibilities**

490     João Firmino-Machado

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

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

496

497     Romeu Mendes

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

500 Study implementation responsibilities: Responsible for study presentation and enrolment of  
501 the primary care units from ACeS Marão e Douro Norte, intervention implementation and data  
502 collection.  
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504 Amélia Moreira  
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506 protocol drafts.  
507 Study implementation responsibilities: Responsible for study presentation and enrolment of  
508 the primary care units from ACeS Porto Oriental, intervention implementation.  
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510 Nuno Lunet  
511 Protocol responsibilities: Conceptual design of the research project and critical review of all  
512 versions of the manuscript.  
513 Study implementation responsibilities: Responsible for the supervision of the study  
514 implementation, data collection and analysis, and writing of the manuscripts.  
515

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523 Name and contacts of funding institutions

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526 Henrique Barros, head of ISPUP: [hbarros@med.up.pt](mailto:hbarros@med.up.pt)

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

### 534 Competing interests

535 All authors have completed the ICMJE uniform disclosure form  
536 at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no organisation influenced the authors  
537 about the decision to submit for publication the current work; no financial relationships with  
538 any organisations that might have an interest in the submitted work in the previous three  
539 years; no other relationships or activities that could appear to have influenced the submitted  
540 work."

541

### 542 Transparency declaration:

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

547

### 548 Figures

549 Legend: † - outcome assessment

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

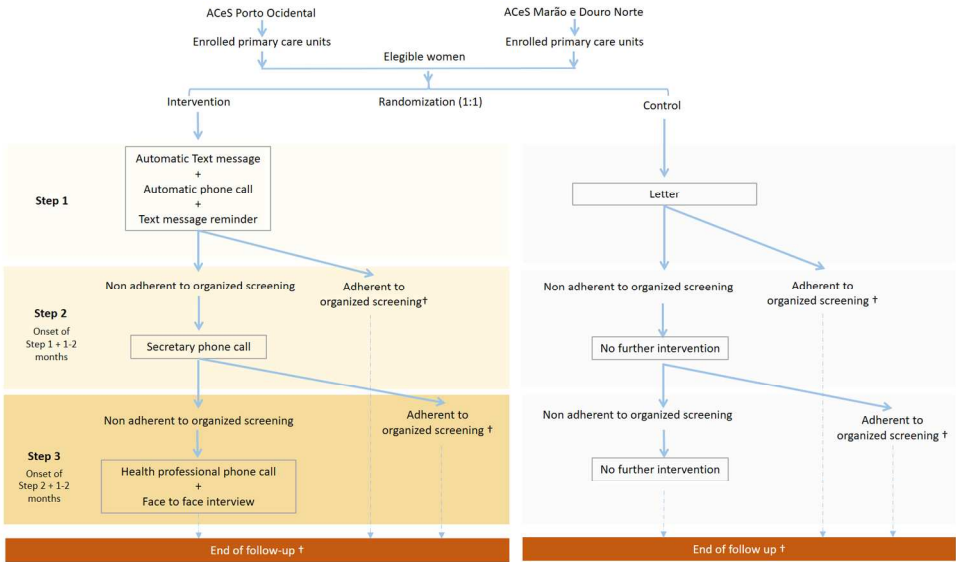
551 Adherence.

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

554 calls.

555 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)

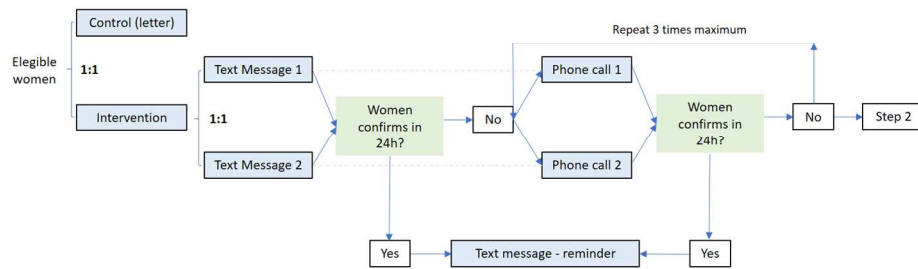


Figure 2 - Flow of Step 1 interventions: written letter, text messages and automated phone calls.

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]?

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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

For peer review only

## 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 is 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.	<p>cancer mortality by 80% and have also reduced the occurrence of new cases of the disease (4).</p> <p>b) Only 6.2% of all pap tests have an abnormal result (5).</p> <p>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).</p> <p>d) The most uncommon abnormal result is HSIL (&lt;1% of all results). From these abnormal results, 1-4% will have an invasive carcinoma (3,5).</p> <p>e) Screening allows early detection of cervical cancer, more attempted treatment and better prognosis.</p> <p>(6)</p>
Screening indication	Women do not perceive they are at risk, because they are too young to start screening or they do not have symptoms.	<p>All women aged between 25 and 60 are recommended to undergo cervical cancer screening every 5 years, except if they (1):</p> <ul style="list-style-type: none"> <li>- Are being treated for cervical cancer</li> <li>- Are hysterectomized</li> <li>- Have not initiated sexual activity</li> <li>- Physical limitation that does not allow a pap test to be performed</li> <li>- Presence of signals or symptoms of gynaecologic disease (active)</li> </ul>
Preference for private health care services	Women prefer to be screened in a private institution, e.g.: by a gynaecologist versus a family doctor	<p>Advantages of an organized cervical cancer screening program (6):</p> <p>a) Higher technical skills and experience of laboratory professionals who read results and classify them</p> <p>b) Frequent quality control verifications</p> <p>c) Standardization of technical procedures</p>

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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](http://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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	7,8
<b>Methods</b>			
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
<b>Randomisation:</b>			
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



1				
2			assessing outcomes) and how	
3				
4		11b	If relevant, description of the similarity of interventions	not applicable
5	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	19
6		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	19
7				
8	<b>Results</b>			
9	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	not applicable (study
10	diagram is strongly		were analysed for the primary outcome	is a protocol)
11	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable (study
12				is a protocol)
13				
14	Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable (study
15				is a protocol)
16		14b	Why the trial ended or was stopped	not applicable (study
17				is a protocol)
18				
19	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable (study
20				is a protocol)
21	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	not applicable (study
22			by original assigned groups	is a protocol)
23				
24	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	not applicable (study
25	estimation		precision (such as 95% confidence interval)	is a protocol)
26		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable (study
27				is a protocol)
28				
29	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	not applicable (study
30			pre-specified from exploratory	is a protocol)
31	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable (study
32				is a protocol)
33				
34	<b>Discussion</b>			
35	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable (study
36				is a protocol)
37	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable (study
38				is a protocol)
39				
40	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable (study
41				is a protocol)
42				

**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](http://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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Oncology, Obstetrics and gynaecology, Health services research, General practice / Family practice
Keywords:	Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

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Manuscripts

**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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## 28 ABSTRACT

### 29 Introduction

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

37 The aim of this study is to assess the effectiveness of a stepwise approach, with increasing  
38 complexity and cost, to improve adherence to organized cervical cancer screening: step 1a-  
39 customized text message invitation;step 1b-customized automated phone call invitation;step  
40 2-secretary phone call;step 3-family health professional phone call and face-to-face  
41 appointment.

### 43 Methods

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

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

56 **Ethics and dissemination**

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

61 **Trial number:**NCT03122275

65 **Number of Words:** 3312

67 **Key Words**

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

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3 71 **STRENGTHS OF THIS STUDY**  
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- 5  
6 72 - Randomized controlled trial, using a stepwise approach, with increasing complexity  
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8 73 and cost of interventions, to improve adherence to organized cervical cancer screening  
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10 74 - Interventions tested are technological and innovative  
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12 75 - Use of a population approach and not specific groups or minorities  
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18 77 **LIMITATIONS OF THIS STUDY**  
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- 20  
21 78 - Contamination of interventions may occur, because randomization units are  
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23 79 individuals and not primary care units  
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25 80 - Unavailability of women's mobile phone may restrict intervention delivery  
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27 81 - The study is restricted to women aged below 50 years, and therefore the findings may  
28  
29 82 not apply to older women with limited digital literacy skills  
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84 INTRODUCTION

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

96 Currently, in Portugal cervical cancer screening is recommended to be performed every 5  
97 years, for women aged between 25 and 65 years old(5). Women registered at a primary care  
98 unit are invited to perform cervical cancer screening through a written letter. At a national  
99 level, just over half(5) of the invited women adhere to the cervical cancer screening and  
100 23.5%(6) have never performed screening during life. Limited adherence to screening is  
101 expected to contribute to greater cervical cancer mortality rates in Portugal (age-standardized  
102 mortality rate: 4.9/100.000)(7), in comparison with the average in Europe's rate (27 countries,  
103 age-standardized mortality rate: 3.7/100.000)(7).

104 Different strategies to increase adherence to cervical cancer screening have been developed  
105 and evaluated, including interventions based on patient reminders (written letters(8–13),  
106 operator dependent phone calls(11,12,14,15) or text messages(16)), small media(17–20)  
107 (videos, brochures, pamphlets or fact sheets), mass media(21) and face-to-face educational  
108 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

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

143

## 144 Objectives

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

148 Step 1a – customized text message invitation;

149 Step 1b – customized automated phone call invitation;

150 Step 2 – secretary phone call;

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

152

153 As primary objectives, we intend to test the superiority of the intervention based on step 1  
154 (1a+1b), and multistage interventions based on steps 1 and 2, and steps 1 to 3.

155

156 The secondary objectives will be the following:

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

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3 167 4. To quantify the differences in adherence to cervical cancer screening when using a  
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5 168 positive or a neutral content of text messages and automated phone calls, in step 1.  
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7 169 5. To estimate the proportion of women who were undergoing performing cervical  
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9 170 cancer screening in private health care services who started to be screened in an  
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11 171 organized cervical cancer screening program, after a health professional face-to-face  
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13 172 appointment at their primary care unit.  
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19 174 Intention-to-treat analysis will be used as primary strategy for all comparisons between  
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21 175 interventions and control. Secondary per-protocol analysis will also be conducted.  
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24 176 The current interventions intend to be inexpensive and easy to implement so they can be used  
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26 177 both in high and low-income countries, at a population level, as strategies to increase the  
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28 178 adherence to cervical cancer screening.  
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## 182 METHODS AND ANALYSIS

### 183 Setting

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

### 191 Design

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

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

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

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

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

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

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

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

206

207 **Participants**

208 Inclusion criteria:

- 209 a) Women aged between 25 and 49 years, and eligible for cervical cancer screening  
210 (having started sexual activity, not hysterectomized, not undergoing cervical cancer  
211 treatment);  
212 b) Medical registration at any of the primary health care units selected for this study;
- 213 Although cervical cancer screening programs are recommended for women with ages till  
214 65 years, will only be considered those that are younger than 50 years because they are  
215 expected to have higher levels of digital literacy and higher use of mobile phones. Data  
216 from 2013 suggests that 99% of the population in the intended age group uses regularly a  
217 mobile phone in comparison with approximately 90% for older age groups(31).

218

219 Exclusion criteria:

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

221

222

223 **Intervention**

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

226

227

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

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

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

238

#### 239 Step 1a – Automated text messages

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

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

250

#### 251 Step 1b – Automated phone calls

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

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254 invitation phone call 1 and 2). Women will receive phone call 1 if they do not answer the  
255 invitation message 1 and receive phone call 2 if they did not answer the invitation message 2.  
256 Women are asked to press the number 1 for appointment confirmation or the number 2 if  
257 they want to receive a phone call from the primary care unit secretary. The audio message will  
258 be repeated three times in the same call, or until women provide the feed-back required.  
259 If women do not answer the phone call or do not press the number 1 or 2, a new automated  
260 phone call will be scheduled for the next day, for a maximum of three days (Figure 2).

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

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

263



264 Step 2 – Secretary phone call

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

272

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

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

286

287 **Outcomes**

288 The primary outcome is defined as follows:

289 Adherence to cervical cancer screening

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

294 The secondary outcomes are defined as follows:

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

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

299 Text message status

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

302 Automated phone call status

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

305 Change from opportunistic to organized screening

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

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

## 312 Sample Size

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

316

### 317 Step 1 (1a+1b)

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

324

### 325 Steps 1 and 2

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

333

### 334 Steps 1 to 3

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

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

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

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

357

## 358 Randomization

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

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

380 **Data collection**

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

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

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

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

393

394 **Statistical analysis**

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

398 a) women who receive the invitation

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

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

402 b) women who have an appointment scheduled:

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

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

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

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

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

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

425

For peer review only



## 426 Ethics and dissemination

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

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

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

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

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

446

447       **REFERENCES**

448       1.     Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global,  
449           regional, and national life expectancy, all-cause mortality, and cause-specific  
450           mortality for 249 causes of death, 1980-2015: a systematic analysis for the  
451           Global Burden of Disease Study 2015. *Lancet* 2016;388:1459–544.

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

453       3.     IARC. Cervical Cancer and Screening. In: *IARC Handbook of Cancer Prevention*,  
454           vol10, Chapter 1. 2005.

455       4.     Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy  
456           of a bivalent L1 virus-like particle vaccine in prevention of infection with human  
457           papillomavirus types 16 and 18 in young women: A randomised controlled trial.  
458           *Lancet* 2004;364: 1757–65.

459       5.     Portuguese Directorate-General of Health. Avaliação e Monitorização dos  
460           Rastreios Oncológicos Organizados de Base Populacional de Portugal  
461           Continental 2014;

462       6.     Oliveira M, Peleteiro B, Lunet N. Cytology use for cervical cancer screening in  
463           Portugal : results from the 2005 / 2006 National Health Survey. *Eur J Public*  
464           Health 2013;1–6.

465       7.     Ferlay J, Steliarova-foucher E, Lortet-tieulent J, Rosso S. Cancer incidence and  
466           mortality patterns in Europe : Estimates for 40 countries in 2012. *Eur J Cancer*  
467           2013;49:1374–403.

468       8.     Lantz PM, Stencil D, Lippert MT, Beversdorf S, Jaros L, Remington PL. Breast and

- 1  
2  
3 469 cervical cancer screening in a low-income managed care sample: The efficacy of  
4  
5 470 physician letters and phone calls. Am J Public Health 1995;85: 834–6.  
6  
7  
8  
9 471 9. Buehler SK, Parsons WL. Effectiveness of a call/recall system in improving  
10  
11 472 compliance with cervical cancer screening: A randomized controlled trial. Cmaj  
12  
13 473 1997;157: 521–6.  
14  
15  
16 474 10. Morrell S, Taylor R, Zeckendorf S, Niciak A, Wain G, Ross J. How much does a  
17  
18 475 reminder letter increase cervical screening among under-screened women in  
19  
20 476 NSW? Aust N Z J Public Health 2005;29: 78–84.  
21  
22  
23  
24 477 11. Eaker S, Adami H, Granath F, Wilander E. A Large Population-Based Randomized  
25  
26 478 Controlled Trial to Increase Attendance at Screening for Cervical Cancer. Cancer  
27  
28 479 Epidemiol Biomarkers Prev 2004;13: 346–55.  
29  
30  
31 480 12. TM V, Glass A, RE G, PA LC, Lichtenstein E. The safety net: a cost-effective  
32  
33 481 approach to improving breast and cervical cancer screening. J Women’s Heal  
34  
35 482 2003;12:789–798.  
36  
37  
38  
39 483 13. Jensen H, Svanholm H, Stovring H, Bro F. A primary healthcare-based  
40  
41 484 intervention to improve a Danish cervical cancer screening programme: a cluster  
42  
43 485 randomised controlled trial. J Epidemiol Community Heal 2009;63:510–5.  
44  
45  
46  
47 486 14. Broberg G, Jonasson JM, Ellis J, Gyrd-Hansen D, Anjemark B, Glantz A, et al.  
48  
49 487 Increasing participation in cervical cancer screening: Telephone contact with  
50  
51 488 long-term non-attendees in Sweden. Results from RACOMIP, a randomized  
52  
53 489 controlled trial. Int J Cancer 2013;133:164–71.  
54  
55  
56  
57 490 15. Women L, Randomized A, Trial C, Dietrich AJ, Tobin JN, Cassells A, et al.  
58  
59  
60

491 Telephone Care Management To Improve Cancer Screening among low-income  
492 women. Ann Intern Med 2006; 563–71.

493 16. Marhayu R, Rashid A, Ramli S, John J. Cost Effective Analysis of Recall Methods  
494 for Cervical Cancer Screening in Selangor - Results from a Prospective  
495 Randomized Controlled Trial. Asian Pac J Cancer Prev 2014;15:1–5.

496 17. Byles JE, Redman S, Sanson-fisher RW, Boyle CA. Effectiveness of two direct-mail  
497 strategies to encourage women to have cervical (Pap) smears. Health Promot Int  
498 1995;10:5–16.

499 18. Rimer BK, Conaway M, Lyna P, Glassman B, Yarnall KSH, Lipkus I, et al. The  
500 impact of tailored interventions on a community health center population.  
501 Patient Educ Couns 1999;37:125–40.

502 19. Taylor VM. A Randomized Controlled Trial of Interventions to Promote Cervical  
503 Cancer Screening Among Chinese Women in North America. Cancer Spectrum  
504 Knowl Environ 2002;94:670–7.

505 20. McAvoy BR, Raza R. Can health education increase uptake of cervical smear  
506 testing among Asian women? BMJ 1991;302:833–6.

507 21. Howe A, Owen-Smith V, Richardson J. The impact of a television soap opera on  
508 the NHS Cervical Screening Programme in the North West of England. J Public  
509 Health Med 2002;24:299–304.

510 22. Valanis BG, Glasgow RE, Mullooly J, Vogt TM, Whitlock EP, Boles SM, et al.  
511 Screening HMO women overdue for both mammograms and pap tests. Prev  
512 Med 2002;34:40–50.

- 1  
2  
3 513 23. Baron RC, Rimer BK, Breslow RA, Coates RJ, Kerner J, Melillo S, et al. Client-  
4  
5 514 Directed Interventions to Increase Community Demand for Breast, Cervical, and  
6  
7 515 Colorectal Cancer Screening - A systematic review. Am J Prev Med 2008;35.  
8  
9  
10 516 24. Arora S, Burner E, Terp S, Nok Lam C, Nercisian A, Bhatt V, et al. Improving  
11  
12 517 attendance at post-emergency department follow-up via automated text  
13  
14 518 message appointment reminders: A randomized controlled trial. Acad Emerg  
15  
16 519 Med 2015;22:31–7.  
17  
18  
19  
20 520 25. Leong KC, Chen WS, Leong KW, Mastura I, Mimi O, Sheikh MA, et al. The use of  
21  
22 521 text messaging to improve attendance in primary care: a randomized controlled  
23  
24 522 trial. Fam Pract 2006;23:699–705.  
25  
26  
27  
28 523 26. Riley WT, Rivera DE, Atienza AA, Nilsen W, Allison SM, Mermelstein R. Health  
29  
30 524 behavior models in the age of mobile interventions: Are our theories up to the  
31  
32 525 task? Transl Behav Med 2011;1:53–71.  
33  
34  
35  
36 526 27. Posadzki P, Mastellos N, Ryan R, Gunn L, Felix L, Pappas Y, et al. Automated  
37  
38 527 telephone communication systems for preventive healthcare and management  
39  
40 528 of long-term conditions. Cochrane database Syst Rev 2016. 2016.  
41  
42  
43  
44 529 28. Hidalgo JL, Sánchez MP, Rabanales J, Simarro MJ, López JL, Campos M.  
45  
46 530 Effectiveness of three interventions in improving adherence to cervical cancer  
47  
48 531 screening 2015;1–7.  
49  
50  
51 532 29. Project F, Paskett ED, Tatum CM, Agostino RD, Rushing J, Velez R, et al.  
52  
53 533 Community-based Interventions to Improve Breast and Cervical Cancer  
54  
55 534 Screening : Results of the Forsyth County Cancer Screening 1999; 8:453–9.  
56  
57  
58  
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58  
59  
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535 30. Direct Extraction from SIARS software, 20/09/2016, at 14:00h.

536 31. Portuguese National Institute of Statistics. Accessed on 15/07/2017, at 16:00h

537 from: [www.ine.pt](http://www.ine.pt).

538 32. Rothman AJ, Bartels RD, Wlaschin J, Salovey P. The strategic use of gain- and

539 loss-framed messages to promote healthy behavior: How theory can inform

540 practice. J Commun 2006; 56:202–20.

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543

544 **OTHER INFORMATION**

545 **Trial registration**

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

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

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550 **Protocol version**

551 11 April 2017. 1st protocol version

552

553 **Roles and responsibilities**

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

555 A description of responsibilities/author can be found below:

556

557 João Firmino-Machado

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

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

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564 Romeu Mendes

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

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

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571 Amélia Moreira

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

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

576

577 Nuno Lunet

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

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

582

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



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595 Henrique Barros, head of ISPUP: [hbarros@med.up.pt](mailto:hbarros@med.up.pt)

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

603 **Competing interests**

604 All authors have completed the ICMJE uniform disclosure form  
605 at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no organisation influenced the authors  
606 about the decision to submit for publication the current work; no financial relationships with  
607 any organisations that might have an interest in the submitted work in the previous three  
608 years; no other relationships or activities that could appear to have influenced the submitted  
609 work."

610

611 **Transparency declaration:**

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

616

617 **Figures**

618 Legend: † - outcome assessment

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

620 Adherence.

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

623 calls.

624 Text Box 1 – Content for text messages and phone calls

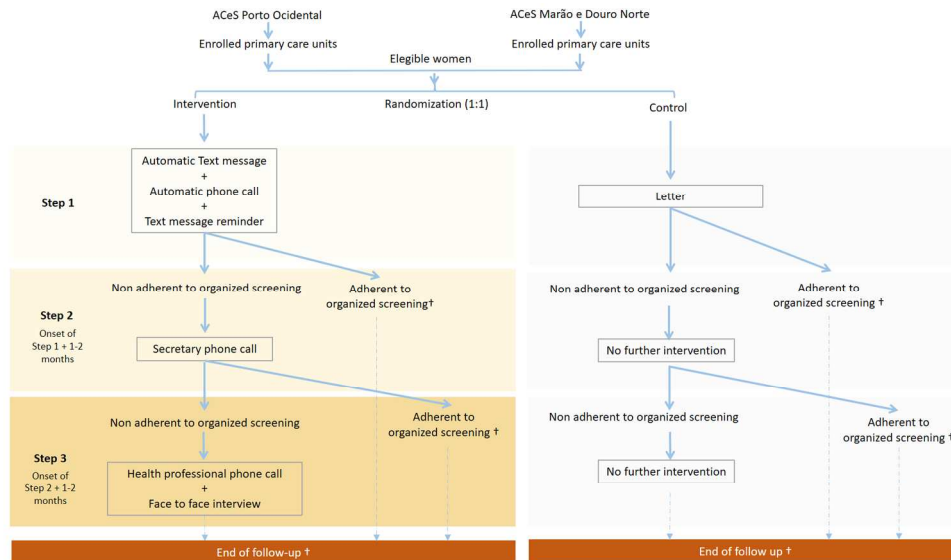


Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.  
Legend: † - outcome assessment

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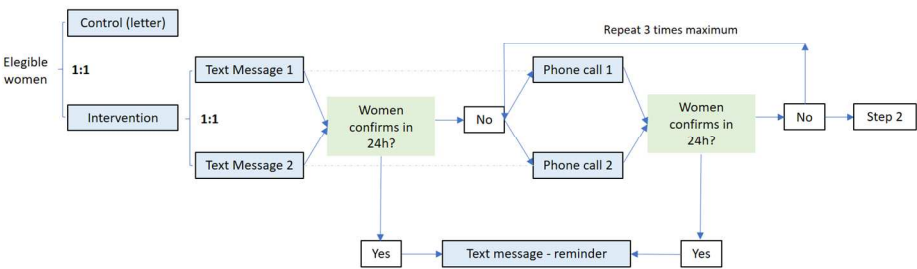


Figure 2 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

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Text Box 1 - Content for text messages and phone calls	
<p><b>Invitation message 1 (neutral framed)</b></p> <p>[FIRST NAME] [LAST NAME]</p> <p>This message is an invitation for cervical cancer screening (Papanicolaou), at your primary care unit [PRIMARY CARE UNIT NAME]</p> <p>Your appointment is scheduled for [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free</p> <p>Answer to this message with the word CONFIRM, to schedule the appointment</p>	<p><b>Invitation message 2 (positively framed)</b></p> <p>[FIRST NAME] [LAST NAME]</p> <p>Keep your cervical cancer screening updated (Papanicolaou)</p> <p>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.</p> <p>Answer to this message with the word CONFIRM, to schedule the appointment</p>
<p><b>Invitation phone call 1 (neutral framed)</b></p> <p>Good evening [FIRST NAME] [LAST NAME], we are calling from your primary care unit [PRIMARY CARE UNIT NAME].</p> <p>This call is an invitation for cervical cancer screening, using a Papanicolaou test.</p> <p>Your appointment is scheduled for [DATE: DD-MM-YYYY], [WEEK DAY], at [HOURS: HH:MM]. Screening and appointment are free.</p> <p>If you are available to attend this appointment press your phone number 1.</p> <p>If you intend to be contacted by your primary care secretary press phone number 2.</p>	<p><b>Invitation phone call 2 (positively framed)</b></p> <p>Good evening [FIRST NAME] [LAST NAME], we are calling from your primary care unit [PRIMARY CARE UNIT NAME].</p> <p>You have the opportunity to update your cancer screening, using Papanicolaou.</p> <p>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.</p> <p>If you are available to attend this appointment press your phone number 1.</p> <p>If you intend to be contacted by your primary care secretary press phone number 2.</p>
<p><b>Reminder message</b></p> <p>[FIRST NAME] [LAST NAME]</p> <p>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]</p>	

Text Box 1 – Content for text messages and phone calls

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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

For peer review only

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 is 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.	<p>cancer mortality by 80% and have also reduced the occurrence of new cases of the disease (4).</p> <p>b) Only 6.2% of all pap tests have an abnormal result (5).</p> <p>c) The most common abnormal result is ASC-US (3.0% of pap tests performed) which corresponds to benign cases requiring only annual follow up (5).</p> <p>d) The most uncommon abnormal result is HSIL (&lt;1% of all results). From these abnormal results, 1-4% will have an invasive carcinoma (3,5).</p> <p>e) Screening allows early detection of cervical cancer, more attempted treatment and better prognosis. (6)</p>
Screening indication	<p>Women do not perceive they are at risk, because they are too young to start screening or they do not have symptoms.</p>	<p>All women aged between 25 and 60 are recommended to undergo cervical cancer screening every 5 years, except if they (1):</p> <ul style="list-style-type: none"><li>- Are being treated for cervical cancer</li><li>- Are hysterectomized</li><li>- Have not initiated sexual activity</li><li>- Physical limitation that does not allow a pap test to be performed</li><li>- Presence of signals or symptoms of gynaecologic disease (active)</li></ul>
Preference for private health care services	<p>Women prefer to be screened in a private institution, e.g.: by a gynaecologist versus a family doctor</p>	<p>Advantages of an organized cervical cancer screening program (6):</p> <p>a) Higher technical skills and experience of laboratory professionals who read results and classify them</p> <p>b) Frequent quality control verifications</p> <p>c) Standardization of technical procedures</p>

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](http://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.



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 <a href="#">Page 1, lines 4-6</a>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">Page 28, lines 539-542</a>
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">All items available on ClinicalTrials.gov, for trial NCT03122275</a>
Protocol version	3	Date and version identifier <a href="#">Page 28, line 545</a>
Funding	4	Sources and types of financial, material, and other support <a href="#">Page 30, lines 574-589</a>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">Page 1, lines 9-15 and pages 28/29, lines 547-572</a>
	5b	Name and contact information for the trial sponsor <a href="#">Page 30, lines 581-584</a>
	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 <a href="#">Page 30, lines 586-589</a>

- 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

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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <a href="#">Not applicable</a>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <a href="#">Not applicable</a>
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 <a href="#">Page 15, lines 283-307</a>
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) <a href="#">Page 10, lines 196-203 + Pages 11-14, lines 222-281</a>
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 <a href="#">Pages 16/17, lines 308-351</a>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <a href="#">Not applicable</a>

**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 <a href="#">Page 18, lines 353-362</a>
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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 <a href="#">Not applicable</a>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions <a href="#">Page 18, lines 358-360</a>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Page 18, lines 362,363</a>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial <a href="#">Not applicable</a>
<b>Methods: Data collection, management, and analysis</b>		
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 <a href="#">Page 19, lines 375-383</a>
	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 <a href="#">Not applicable</a>
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 <a href="#">Page 19, lines 384-387</a>

1			
2	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
3	methods		Reference to where other details of the statistical analysis plan can be
4			found, if not in the protocol
5			<a href="#">Page 20, lines 402-404</a>
6			
7			
8			
9		20b	Methods for any additional analyses (eg, subgroup and adjusted
10			analyses)
11			<a href="#">Page 20, lines 405-414</a>
12			
13		20c	Definition of analysis population relating to protocol non-adherence
14			(eg, as randomised analysis), and any statistical methods to handle
15			missing data (eg, multiple imputation)
16			<a href="#">Page 20, lines 390-401 and page 21, lines 415-417</a>
17			
18			
19			
20			
21	<b>Methods: Monitoring</b>		
22			
23	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
24			and reporting structure; statement of whether it is independent from
25			the sponsor and competing interests; and reference to where further
26			details about its charter can be found, if not in the protocol.
27			Alternatively, an explanation of why a DMC is not needed
28			<a href="#">Not applicable – DMC is considered unnecessary due to the nature of</a>
29			<a href="#">the intervention</a>
30			
31			
32		21b	Description of any interim analyses and stopping guidelines, including
33			who will have access to these interim results and make the final
34			decision to terminate the trial
35			<a href="#">Not applicable</a>
36			
37			
38			
39	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
40			spontaneously reported adverse events and other unintended effects
41			of trial interventions or trial conduct
42			<a href="#">Not applicable</a>
43			
44			
45			
46	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
47			whether the process will be independent from investigators and the
48			sponsor
49			<a href="#">Not applicable</a>
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## Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval <a href="#">Page 22, lines 422-424</a>
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) <a href="#">Not applicable</a>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) <a href="#">Page 22, lines 426-432</a>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable <a href="#">Not applicable</a>
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 <a href="#">Page 19, lines 384-387</a>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site <a href="#">Page 31, lines 593-598</a>
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 <a href="#">Page 19, lines 384-386</a>
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 <a href="#">Not applicable</a>

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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 – <a href="#">Page 22, lines 436-440</a>
	31b	Authorship eligibility guidelines and any intended use of professional writers <a href="#">Page 28/29, lines 548-573</a>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <a href="#">Not applicable</a>
<b>Appendices</b>		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <a href="#">See attached documents: informed consent</a>
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 <a href="#">No applicable</a>

\*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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	7,8
<b>Methods</b>			
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

1			assessing outcomes) and how	
2		11b	If relevant, description of the similarity of interventions	not applicable
3	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	19
4		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	19
5				
6	<b>Results</b>			
7	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	not applicable (study
8	diagram is strongly		were analysed for the primary outcome	is a protocol)
9	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	not applicable (study
10				is a protocol)
11				
12	Recruitment	14a	Dates defining the periods of recruitment and follow-up	not applicable (study
13				is a protocol)
14		14b	Why the trial ended or was stopped	not applicable (study
15				is a protocol)
16				
17	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	not applicable (study
18				is a protocol)
19				
20	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	not applicable (study
21			by original assigned groups	is a protocol)
22				
23	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	not applicable (study
24	estimation		precision (such as 95% confidence interval)	is a protocol)
25		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable (study
26				is a protocol)
27				
28	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	not applicable (study
29			pre-specified from exploratory	is a protocol)
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31	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable (study
32				is a protocol)
33				
34	<b>Discussion</b>			
35	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable (study
36				is a protocol)
37				
38	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	not applicable (study
39				is a protocol)
40				
41	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable (study
42				is a protocol)
43				

**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](http://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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<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Oncology, Obstetrics and gynaecology, Health services research, General practice / Family practice
Keywords:	Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging, Reminder Systems, Directive Counselling

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Manuscripts

**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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## 28 ABSTRACT

### 29 Introduction

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

37 The aim of this study is to assess the effectiveness of a stepwise approach, with increasing  
38 complexity and cost, to improve adherence to organized cervical cancer screening: step 1a-  
39 customized text message invitation;step 1b-customized automated phone call invitation;step  
40 2-secretary phone call;step 3-family health professional phone call and face-to-face  
41 appointment.

### 43 Methods

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



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3 51 The secondary outcomes are: proportion of women screened after each step(1a,2 and 3);  
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5 52 proportion of text messages/phone calls delivered; proportion of women previously screened  
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7 53 in a private health institution who change to organized screening. The intervention and control  
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9 54 groups will be compared based on intention-to-treat and per protocol analyses.  
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15 56 **Ethics and dissemination**

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18 57 The study was approved by the Ethics Committee of the Northern Health Region  
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20 58 Administration and National Data Protection Committee. Results will be disseminated through  
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22 59 communications in scientific meetings and peer-reviewed journals.  
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28 61 **Trial number:**NCT03122275  
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38 65 **Number of Words:** 3312  
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44 67 **Key Words**

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46 68 Mass Screening, Early Detection of Cancer, Uterine Cervical Neoplasms, Text Messaging,  
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48 69 Reminder Systems, Directive Counselling  
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3 71 **STRENGTHS OF THIS STUDY**  
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6 72 - Randomized controlled trial, using a stepwise approach, with increasing complexity  
7  
8 73 and cost of interventions, to improve adherence to organized cervical cancer screening  
9  
10 74 - Interventions tested are technological and innovative  
11  
12 75 - Use of a population approach and not specific groups or minorities  
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18 77 **LIMITATIONS OF THIS STUDY**  
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- 20  
21 78 - Contamination of interventions may occur, because randomization units are  
22  
23 79 individuals and not primary care units  
24  
25 80 - Unavailability of women's mobile phone may restrict intervention delivery  
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27 81 - The study is restricted to women aged below 50 years, and therefore the findings may  
28  
29 82 not apply to older women with limited digital literacy skills  
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84 INTRODUCTION

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

96 Currently, in Portugal cervical cancer screening is recommended to be performed every 5  
97 years, for women aged between 25 and 65 years old(5). Women registered at a primary care  
98 unit are invited to perform cervical cancer screening through a written letter. At a national  
99 level, just over half(5) of the invited women adhere to the cervical cancer screening and  
100 23.5%(6) have never performed screening during life. Limited adherence to screening is  
101 expected to contribute to greater cervical cancer mortality rates in Portugal (age-standardized  
102 mortality rate: 4.9/100.000)(7), in comparison with the average in Europe's rate (27 countries,  
103 age-standardized mortality rate: 3.7/100.000)(7).

104 Different strategies to increase adherence to cervical cancer screening have been developed  
105 and evaluated, including interventions based on patient reminders (written letters(8–13),  
106 operator dependent phone calls(11,12,14,15) or text messages(16)), small media(17–20)  
107 (videos, brochures, pamphlets or fact sheets), mass media(21) and face-to-face educational  
108 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

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

143

## 144 Objectives

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

148 Step 1a – customized text message invitation;

149 Step 1b – customized automated phone call invitation;

150 Step 2 – secretary phone call;

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

152

153 As primary objectives, we intend to test the superiority of the intervention based on step 1  
154 (1a+1b), and multistage interventions based on steps 1 and 2, and steps 1 to 3.

155

156 The secondary objectives will be the following:

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

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167 4. To quantify the differences in adherence to cervical cancer screening when using a  
168 positive or a neutral content of text messages and automated phone calls, in step 1.  
169 5. To estimate the proportion of women who were undergoing performing cervical  
170 cancer screening in private health care services who started to be screened in an  
171 organized cervical cancer screening program, after a health professional face-to-face  
172 appointment at their primary care unit.  
173  
174 Intention-to-treat analysis will be used as primary strategy for all comparisons between  
175 interventions and control. Secondary per-protocol analysis will also be conducted.  
176 The current interventions intend to be inexpensive and easy to implement so they can be used  
177 both in high and low-income countries, at a population level, as strategies to increase the  
178 adherence to cervical cancer screening.  
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181

## 182 METHODS AND ANALYSIS

### 183 Setting

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

### 191 Design

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

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

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

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

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

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

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



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

206

207 **Participants**

208 Inclusion criteria:

- 209 a) Women aged between 25 and 49 years, and eligible for cervical cancer screening  
210 (having started sexual activity, not hysterectomized, not undergoing cervical cancer  
211 treatment);  
212 b) Medical registration at any of the primary health care units selected for this study.

213 Although cervical cancer screening programs are recommended for women with ages till  
214 65 years, will only be considered for this study those younger than 50 years, who are  
215 expected to have higher levels of digital literacy, and therefore more likely to benefit from  
216 this type of intervention. Nevertheless, this may limit the possibility of generalising our  
217 findings to older women who are less proficient in the use of mobile technology.

218

219 Exclusion criteria:

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

221

222

223 **Intervention**

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

226

227

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

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

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

238

#### 239 Step 1a – Automated text messages

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

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

250

#### 251 Step 1b – Automated phone calls

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

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254 invitation phone call 1 and 2). Women will receive phone call 1 if they do not answer the  
255 invitation message 1 and receive phone call 2 if they did not answer the invitation message 2.  
256 Women are asked to press the number 1 for appointment confirmation or the number 2 if  
257 they want to receive a phone call from the primary care unit secretary. The audio message will  
258 be repeated three times in the same call, or until women provide the feed-back required.  
259 If women do not answer the phone call or do not press the number 1 or 2, a new automated  
260 phone call will be scheduled for the next day, for a maximum of three days (Figure 3).

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

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

263

264 Step 2 – Secretary phone call

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

272

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

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

286

287 **Outcomes**

288 The primary outcome is defined as follows:

289 Adherence to cervical cancer screening

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

294 The secondary outcomes are defined as follows:

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

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

299 Text message status

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

302 Automated phone call status

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

305 Change from opportunistic to organized screening

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

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

## 312 Sample Size

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

316

### 317 Step 1 (1a+1b)

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

324

### 325 Steps 1 and 2

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

333

### 334 Steps 1 to 3

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

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3 337 increase in comparison to the expected adherence after steps 2, from 45 to 50%, may be  
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5 338 anticipated due to the longer period between baseline and outcome assessment. The  
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7 339 magnitude of increase in adherence in the intervention group, was estimated based on the  
8  
9 340 previously observed effectiveness of face-to-face appointments in other settings.(20). The  
10  
11 341 minimum sample size determined for each group is 134 women.  
12  
13  
14 342 The overall sample size needed is 1038 (519\*2), determined by step 1 interventions, since the  
15  
16 343 remaining primary outcomes require a smaller sample size. Nevertheless, a 10% greater  
17  
18 344 number of participants will be recruited to account for the potential withdrawal of one health  
19  
20 345 care unit before the completion of the stepwise intervention. We anticipate that the drop-out  
21  
22 346 of individual participants will be lower than 1%, during the steps 2 and 3 of the intervention;  
23  
24 347 this low value is expected because we will use an opt-out strategy, so that only women who  
25  
26 348 actively express their willingness for not receiving further interventions are considered as  
27  
28 349 drop-outs.  
29  
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31  
32 350 The statistical analysis for accomplishment of secondary objectives are exploratory and  
33  
34 351 therefore the sample size was not determined to consider them. Nevertheless, the sample size  
35  
36 352 defined for the study, is expected to have enough power to test the superiority of the isolate  
37  
38 353 effect of step 1b, step 2 or step 3. Additionally, the sample size is also enough to test non-  
39  
40 354 inferiority secondary objectives, assuming one-sided tests, a significance level of 2.5%, power  
41  
42 355 of 90%, an adherence proportion in control group of 40% and 50% in experimental group and a  
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44 356 non-inferiority limit of 5%.  
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## 358 Randomization

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

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



380     **Data collection**

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

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

387     Sociodemographic characteristics, including age, education level, parity, marital and  
388     employment status and type of job will be manually extracted from the electronic medical  
389     record (EMR). Age and parity will be collected as continuous variables and all the others as  
390     categorical. Education level will comprise the categories lower than 9 years of education, 9 to  
391     11 years, 12 or more years. Marital status will be coded as single, married or divorced.  
392     Employment status will be defined as student, employed, unemployed or retired and the  
393     occupation as upper white collar, lower white collar, high skilled blue collar and low skilled  
394     blue collar.

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

399

## 400 Statistical analysis

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

404 a) women who receive the invitation

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

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

408 b) women who have an appointment scheduled:

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

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

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

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

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

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

431

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## 432 Ethics and dissemination

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

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

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

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

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

452

453       **REFERENCES**

454       1.       Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global,  
455               regional, and national life expectancy, all-cause mortality, and cause-specific  
456               mortality for 249 causes of death, 1980-2015: a systematic analysis for the  
457               Global Burden of Disease Study 2015. *Lancet* 2016;388:1459–544.

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

459       3.       IARC. Cervical Cancer and Screening. In: *IARC Handbook of Cancer Prevention*,  
460               vol10, Chapter 1. 2005.

461       4.       Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy  
462               of a bivalent L1 virus-like particle vaccine in prevention of infection with human  
463               papillomavirus types 16 and 18 in young women: A randomised controlled trial.  
464               *Lancet* 2004;364: 1757–65.

465       5.       Portuguese Directorate-General of Health. Avaliação e Monitorização dos  
466               Rastreios Oncológicos Organizados de Base Populacional de Portugal  
467               Continental 2014;

468       6.       Oliveira M, Peleteiro B, Lunet N. Cytology use for cervical cancer screening in  
469               Portugal : results from the 2005 / 2006 National Health Survey. *Eur J Public*  
470               Health 2013;1–6.

471       7.       Ferlay J, Steliarova-foucher E, Lortet-tieulent J, Rosso S. Cancer incidence and  
472               mortality patterns in Europe : Estimates for 40 countries in 2012. *Eur J Cancer*  
473               2013;49:1374–403.

474       8.       Lantz PM, Stencil D, Lippert MT, Beversdorf S, Jaros L, Remington PL. Breast and

- 1  
2  
3 475 cervical cancer screening in a low-income managed care sample: The efficacy of  
4  
5 476 physician letters and phone calls. Am J Public Health 1995;85: 834–6.  
6  
7  
8  
9 477 9. Buehler SK, Parsons WL. Effectiveness of a call/recall system in improving  
10  
11 478 compliance with cervical cancer screening: A randomized controlled trial. Cmaj  
12  
13 479 1997;157: 521–6.  
14  
15  
16 480 10. Morrell S, Taylor R, Zeckendorf S, Niciak A, Wain G, Ross J. How much does a  
17  
18 481 reminder letter increase cervical screening among under-screened women in  
19  
20 482 NSW? Aust N Z J Public Health 2005;29: 78–84.  
21  
22  
23  
24 483 11. Eaker S, Adami H, Granath F, Wilander E. A Large Population-Based Randomized  
25  
26 484 Controlled Trial to Increase Attendance at Screening for Cervical Cancer. Cancer  
27  
28 485 Epidemiol Biomarkers Prev 2004;13: 346–55.  
29  
30  
31 486 12. TM V, Glass A, RE G, PA LC, Lichtenstein E. The safety net: a cost-effective  
32  
33 487 approach to improving breast and cervical cancer screening. J Women's Heal  
34  
35 488 2003;12:789–798.  
36  
37  
38  
39 489 13. Jensen H, Svanholm H, Stovring H, Bro F. A primary healthcare-based  
40  
41 490 intervention to improve a Danish cervical cancer screening programme: a cluster  
42  
43 491 randomised controlled trial. J Epidemiol Community Heal 2009;63:510–5.  
44  
45  
46  
47 492 14. Broberg G, Jonasson JM, Ellis J, Gyrd-Hansen D, Anjemark B, Glantz A, et al.  
48  
49 493 Increasing participation in cervical cancer screening: Telephone contact with  
50  
51 494 long-term non-attendees in Sweden. Results from RACOMIP, a randomized  
52  
53 495 controlled trial. Int J Cancer 2013;133:164–71.  
54  
55  
56  
57 496 15. Women L, Randomized A, Trial C, Dietrich AJ, Tobin JN, Cassells A, et al.  
58  
59  
60

497 Telephone Care Management To Improve Cancer Screening among low-income  
498 women. Ann Intern Med 2006; 563–71.

499 16. Marhayu R, Rashid A, Ramli S, John J. Cost Effective Analysis of Recall Methods  
500 for Cervical Cancer Screening in Selangor - Results from a Prospective  
501 Randomized Controlled Trial. Asian Pac J Cancer Prev 2014;15:1–5.

502 17. Byles JE, Redman S, Sanson-fisher RW, Boyle CA. Effectiveness of two direct-mail  
503 strategies to encourage women to have cervical (Pap) smears. Health Promot Int  
504 1995;10:5–16.

505 18. Rimer BK, Conaway M, Lyna P, Glassman B, Yarnall KSH, Lipkus I, et al. The  
506 impact of tailored interventions on a community health center population.  
507 Patient Educ Couns 1999;37:125–40.

508 19. Taylor VM. A Randomized Controlled Trial of Interventions to Promote Cervical  
509 Cancer Screening Among Chinese Women in North America. CancerSpectrum  
510 Knowl Environ 2002;94:670–7.

511 20. McAvoy BR, Raza R. Can health education increase uptake of cervical smear  
512 testing among Asian women? BMJ 1991;302:833–6.

513 21. Howe A, Owen-Smith V, Richardson J. The impact of a television soap opera on  
514 the NHS Cervical Screening Programme in the North West of England. J Public  
515 Health Med 2002;24:299–304.

516 22. Valanis BG, Glasgow RE, Mullooly J, Vogt TM, Whitlock EP, Boles SM, et al.  
517 Screening HMO women overdue for both mammograms and pap tests. Prev  
518 Med 2002;34:40–50.

- 1  
2  
3 519 23. Baron RC, Rimer BK, Breslow RA, Coates RJ, Kerner J, Melillo S, et al. Client-  
4  
5 520 Directed Interventions to Increase Community Demand for Breast, Cervical, and  
6  
7 521 Colorectal Cancer Screening - A systematic review. Am J Prev Med 2008;35.  
8  
9  
10  
11 522 24. Arora S, Burner E, Terp S, Nok Lam C, Nercisian A, Bhatt V, et al. Improving  
12  
13 523 attendance at post-emergency department follow-up via automated text  
14  
15 524 message appointment reminders: A randomized controlled trial. Acad Emerg  
16  
17 525 Med 2015;22:31–7.  
18  
19  
20  
21 526 25. Leong KC, Chen WS, Leong KW, Mastura I, Mimi O, Sheikh MA, et al. The use of  
22  
23 527 text messaging to improve attendance in primary care: a randomized controlled  
24  
25 528 trial. Fam Pract 2006;23:699–705.  
26  
27  
28 529 26. Riley WT, Rivera DE, Atienza AA, Nilsen W, Allison SM, Mermelstein R. Health  
29  
30 530 behavior models in the age of mobile interventions: Are our theories up to the  
31  
32 531 task? Transl Behav Med 2011;1:53–71.  
33  
34  
35  
36 532 27. Posadzki P, Mastellos N, Ryan R, Gunn L, Felix L, Pappas Y, et al. Automated  
37  
38 533 telephone communication systems for preventive healthcare and management  
39  
40 534 of long-term conditions. Cochrane database Syst Rev 2016. 2016.  
41  
42  
43  
44 535 28. Hidalgo JL, Sánchez MP, Rabanales J, Simarro MJ, López JL, Campos M.  
45  
46 536 Effectiveness of three interventions in improving adherence to cervical cancer  
47  
48 537 screening 2015;1–7.  
49  
50  
51 538 29. Project F, Paskett ED, Tatum CM, Agostino RD, Rushing J, Velez R, et al.  
52  
53 539 Community-based Interventions to Improve Breast and Cervical Cancer  
54  
55 540 Screening : Results of the Forsyth County Cancer Screening 1999; 8:453–9.  
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52  
53  
54  
55  
56  
57  
58  
59  
60

541 30. Direct Extraction from SIARS software, 20/09/2016, at 14:00h.

542 31. Rothman AJ, Bartels RD, Wlaschin J, Salovey P. The strategic use of gain- and

543 loss-framed messages to promote healthy behavior: How theory can inform

544 practice. J Commun 2006; 56:202–20.

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For peer review only

548 **OTHER INFORMATION**

549 **Trial registration**

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

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

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553

554 **Protocol version**

555 11 April 2017. 1st protocol version

556

557 **Roles and responsibilities**

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

559 A description of responsibilities/author can be found below:

560

561 João Firmino-Machado

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

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

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568 Romeu Mendes

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569 Protocol responsibilities: Conceptual design of the research project and critical review of the  
570 manuscript.  
  
571 Study implementation responsibilities: Responsible for study presentation and enrolment of  
572 the primary care units from ACeS Marão e Douro Norte, intervention implementation and data  
573 collection.  
  
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576 Protocol responsibilities: Conceptual design of the research project and critical review of all  
577 protocol drafts.  
  
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582 Protocol responsibilities: Conceptual design of the research project and critical review of all  
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584 Study implementation responsibilities: Responsible for the supervision of the study  
585 implementation, data collection and analysis, and writing of the manuscripts.  
  
586  
  
587 All the authors gave a final approval of the version to be published and agreed to be  
588 accountable for all aspects of the work.

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599 Henrique Barros, head of ISPUP: [hbarros@med.up.pt](mailto:hbarros@med.up.pt)

600

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

605

606

607 **Competing interests**

608 All authors have completed the ICMJE uniform disclosure form  
609 at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no organisation influenced the authors  
610 about the decision to submit for publication the current work; no financial relationships with  
611 any organisations that might have an interest in the submitted work in the previous three  
612 years; no other relationships or activities that could appear to have influenced the submitted  
613 work."

614

615 **Transparency declaration:**

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

620

621 **Figures**

622 Legend: † - outcome assessment

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

624 Adherence.

625 Figure 2 – Content for text messages and phone calls.

626

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

628 calls.

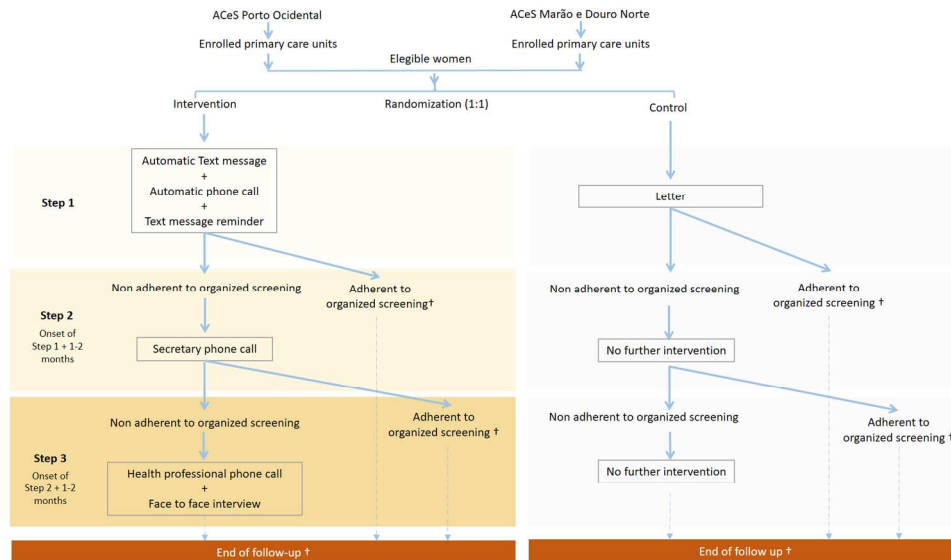


Figure 1 – Study design of the Stepwise Strategy to Improve Cervical Cancer Screening Adherence.  
Legend: † - outcome assessment

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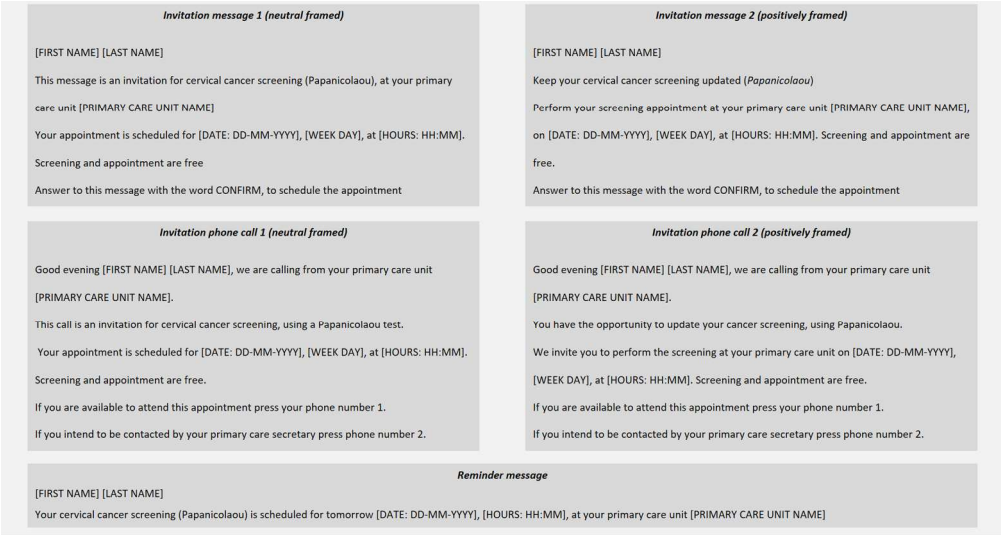


Figure 2 – Content for text messages and phone calls.

162x86mm (300 x 300 DPI)

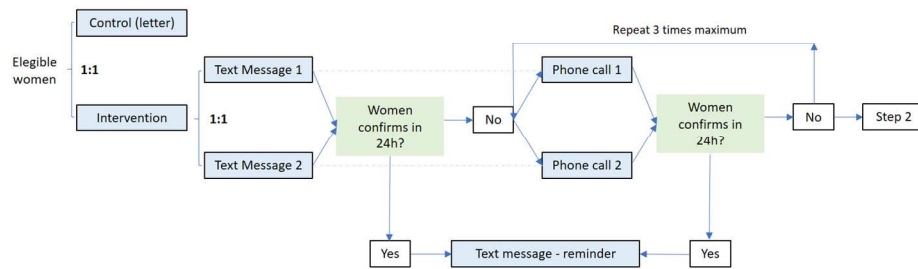


Figure 3 – Flow of Step 1 interventions: written letter, text messages and automated phone calls.

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

For peer review only

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 is 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.	<p>cancer mortality by 80% and have also reduced the occurrence of new cases of the disease (4).</p> <p>b) Only 6.2% of all pap tests have an abnormal result (5).</p> <p>c) The most common abnormal result is ASC-US (3.0% of pap tests performed) which corresponds to benign cases requiring only annual follow up (5).</p> <p>d) The most uncommon abnormal result is HSIL (&lt;1% of all results). From these abnormal results, 1-4% will have an invasive carcinoma (3,5).</p> <p>e) Screening allows early detection of cervical cancer, more attempted treatment and better prognosis. (6)</p>
Screening indication	<p>Women do not perceive they are at risk, because they are too young to start screening or they do not have symptoms.</p>	<p>All women aged between 25 and 60 are recommended to undergo cervical cancer screening every 5 years, except if they (1):</p> <ul style="list-style-type: none"><li>- Are being treated for cervical cancer</li><li>- Are hysterectomized</li><li>- Have not initiated sexual activity</li><li>- Physical limitation that does not allow a pap test to be performed</li><li>- Presence of signals or symptoms of gynaecologic disease (active)</li></ul>
Preference for private health care services	<p>Women prefer to be screened in a private institution, e.g.: by a gynaecologist versus a family doctor</p>	<p>Advantages of an organized cervical cancer screening program (6):</p> <p>a) Higher technical skills and experience of laboratory professionals who read results and classify them</p> <p>b) Frequent quality control verifications</p> <p>c) Standardization of technical procedures</p>

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](http://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.



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

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <a href="#">Page 1, lines 4-6</a>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">Page 28, lines 539-542</a>
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">All items available on ClinicalTrials.gov, for trial NCT03122275</a>
Protocol version	3	Date and version identifier <a href="#">Page 28, line 545</a>
Funding	4	Sources and types of financial, material, and other support <a href="#">Page 30, lines 574-589</a>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">Page 1, lines 9-15 and pages 28/29, lines 547-572</a>
	5b	Name and contact information for the trial sponsor <a href="#">Page 30, lines 581-584</a>
	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 <a href="#">Page 30, lines 586-589</a>

- 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



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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <a href="#">Not applicable</a>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <a href="#">Not applicable</a>
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 <a href="#">Page 15, lines 283-307</a>
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) <a href="#">Page 10, lines 196-203 + Pages 11-14, lines 222-281</a>
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 <a href="#">Pages 16/17, lines 308-351</a>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <a href="#">Not applicable</a>

**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 <a href="#">Page 18, lines 353-362</a>
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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 <a href="#">Not applicable</a>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions <a href="#">Page 18, lines 358-360</a>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <a href="#">Page 18, lines 362,363</a>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial <a href="#">Not applicable</a>
<b>Methods: Data collection, management, and analysis</b>		
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 <a href="#">Page 19, lines 375-383</a>
	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 <a href="#">Not applicable</a>
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 <a href="#">Page 19, lines 384-387</a>

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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 <a href="#">Page 20, lines 402-404</a>
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) <a href="#">Page 20, lines 405-414</a>
	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) <a href="#">Page 20, lines 390-401 and page 21, lines 415-417</a>
<b>Methods: Monitoring</b>		
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 <a href="#">Not applicable – DMC is considered unnecessary due to the nature of the intervention</a>
	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 <a href="#">Not applicable</a>
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 <a href="#">Not applicable</a>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor <a href="#">Not applicable</a>

## Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval <a href="#">Page 22, lines 422-424</a>
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) <a href="#">Not applicable</a>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) <a href="#">Page 22, lines 426-432</a>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable <a href="#">Not applicable</a>
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 <a href="#">Page 19, lines 384-387</a>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site <a href="#">Page 31, lines 593-598</a>
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 <a href="#">Page 19, lines 384-386</a>
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 <a href="#">Not applicable</a>

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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 – <a href="#">Page 22, lines 436-440</a>
	31b	Authorship eligibility guidelines and any intended use of professional writers <a href="#">Page 28/29, lines 548-573</a>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <a href="#">Not applicable</a>
<b>Appendices</b>		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <a href="#">See attached documents: informed consent</a>
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 <a href="#">No applicable</a>

\*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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	7,8
<b>Methods</b>			
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

1		assessing outcomes) and how	
2		11b If relevant, description of the similarity of interventions	not applicable
3	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	19
4		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	19
5			
6	<b>Results</b>		
7	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	not applicable (study
8	diagram is strongly	were analysed for the primary outcome	is a protocol)
9	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	not applicable (study
10			is a protocol)
11			
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	not applicable (study
13			is a protocol)
14		14b Why the trial ended or was stopped	not applicable (study
15			is a protocol)
16			
17	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	not applicable (study
18			is a protocol)
19			
20	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	not applicable (study
21		by original assigned groups	is a protocol)
22			
23	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	not applicable (study
24	estimation	precision (such as 95% confidence interval)	is a protocol)
25		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	not applicable (study
26			is a protocol)
27			
28	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	not applicable (study
29		pre-specified from exploratory	is a protocol)
30			
31	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	not applicable (study
32			is a protocol)
33			
34	<b>Discussion</b>		
35	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	not applicable (study
36			is a protocol)
37			
38	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	not applicable (study
39			is a protocol)
40			
41	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	not applicable (study
42			is a protocol)
43			

**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](http://www.consort-statement.org).