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A 3-step intervention to improve adherence to cervical cancer screening: The SCAN randomized controlled trial

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ABSTRACT

The aim of this study was to test the effectiveness of a stepwise intervention with an increasing level of complexity and cost to increase adherence to organized cervical cancer screening. This was a randomized (1: 1) controlled trial, conducted among 13 Portuguese primary health care units. Participants (n = 1220) were women aged 25–49 years, eligible for cervical cancer screening, with a mobile phone number available. The tested intervention was a 3-step invitation to screening, based on automated text messages/phone calls (step 1), manual phone calls (step 2) and face-to-face interviews (step 3), applied sequentially to non-adherent women after each step. Participants in the control group were invited through a written letter (standard of care). The primary outcome was the proportion of women screened, which was assessed after step 1 (45 days after the initial invitation), steps 1 + 2 (90 days after the initial invitation) and steps 1 + 2 + 3 (150 days after the initial invitation). Adherence to cervical cancer screening was significantly higher among women assigned to the intervention than those in the control group for step 1 (39.9% vs. 25.7%, $p < 0.001$), steps 1 + 2 (48.6% vs. 30.7%, $p < 0.001$) and steps 1 + 2 + 3 (51.2% vs. 34.0%, $p < 0.001$). In conclusion, adherence to cervical cancer screening was higher by 17% among women invited through the 3-step intervention, compared to those receiving the standard invitation letter. The former strategy has the potential to be broadly implemented due to the low requirements of technology and training.

Clinical Trial Registration: NCT03122275

1. Background

Healthcare costs are increasing 1.4 times faster than economic growth across low and high-income countries, which may compromise access to care in the long term (World Health Organization, 2017). High performance health systems are therefore needed for a sustainable balance between expenditure and the required innovation, service quality and patient safety (Fineberg, 2012). This may be achieved through measures that include patient-centred care, improvements in information technology systems, waste reduction strategies or an increased focus on prevention (Fineberg, 2012; OECD, 2017; *The value of health improving outcomes*, 2016).

Cancer is the second cause of death worldwide and accounts for an expenditure of 1.5% of the global gross domestic product (American Cancer

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Society, 2010). Strategies to reduce its morbidity and mortality burden include organized screening programs that promote early detection and treatment, namely those targeting breast, colorectal and cervical cancers (The International Bank for Reconstruction and Development/The World Bank, 2006). Despite the broad implementation of cancer screening, adherence is often low, which contributes to a sub-optimal use of the resources allocated to these services (European Comission, 2017). Therefore, affordable strategies are required to increase the population's participation in organized screening (Baron et al., 2008; Duffy et al., 2017; Lu et al., 2012). This may be achieved through the combination of extremely low-cost methods, such as invitations using automated text messages or phone calls, which may increase adherence by up to 15% (Posadzki et al., 2016; Uy et al., 2017), and interventions requiring an increasing level of tailoring and customization, for the remaining non-adherent participants. Manual phone calls, although with high costs per invitation have been described to increase adherence by 20% in a population previously non-adherent to screening after a strategy based on a written letter and a reminder (Eaker et al., 2004). Previous studies that evaluated such stepwise approaches targeted only deprived (Lantz et al., 1995) or non-adherent (Vogt et al., 2003) women, did not test automated nor extremely low-cost interventions (Eaker et al., 2004; Lantz et al., 1995; Vogt et al., 2003) and interventions had no clear gradient of customization and complexity (Eaker et al., 2004; Lantz et al., 1995; Vogt et al., 2003).

Therefore, we aimed to assess the effectiveness of an intervention, with gradually increasing complexity and cost (automated text messages/phone calls, manual phone calls and face-to-face interviews), to improve the adherence to organized cancer screening, in relation to the standard of care.

2. Materials and methods

A stepwise strategy to increase adherence to cervical cancer screening was assessed in a multicentre, parallel, population-based randomized controlled trial (*Stepwise strategy to improve cervical cancer screening adherence* – SCAN-Cervical Cancer). The invitation was initially performed through automated and customized text messages, phone calls and reminders (step 1). Non-adherent participants after step 1 were then invited through phone calls performed by clinical secretaries (step 2), and those remaining non-adherent after steps 1 + 2 were also invited through phone calls and face-to-face appointments conducted by medical doctors (step 3). The study protocol was previously published, as have the results from step 1 (Firmino-Machado et al., 2017; Firmino-Machado et al., 2018). Here we report the effect of an invitation based on steps 1 + 2 and steps 1 + 2 + 3, as well as the isolate effect of step 2 and step 3, in relation to the standard of care.

2.1. Setting and participants

In Portugal, the National Health System provides universal and essentially free of charge access to treatment, but also to preventive services, such as screening. Organized cervical cancer screening is implemented by the primary health care units, and accomplished through systematic written letter invitations, every five years, to women aged 25–65 years and having no history of total hysterectomy, diagnosis of cervical cancer, or gynaecologic signs or symptoms (Ministry of Health, 2017).

Women eligible for cervical cancer screening may be enrolled in organized programs, in the areas where they are available, or opportunistically invited for testing by their medical doctor during appointments scheduled for other health purposes. Opportunistic screening may also take place during medical appointments in the private sector.

The SCAN trial included women aged 25–49 years, eligible for cervical cancer screening and registered at the primary health care units involved in organized screening. A total of 27 women with no mobile phone number registered at administrative health records were excluded, despite fulfilling the remaining eligibility criteria.

This study was conducted in two primary Health Care Areas in Portugal: *Porto Ocidental* (urban area), with an adherence to cervical cancer screening of 30% (*Direct extraction from the Portuguese software to monitor organized screening (SIARS)*, n.d.), and *Marão e Douro Norte* (sub-urban and rural area), with an adherence to cervical cancer screening estimated at 60% (*Direct extraction from the Portuguese software to monitor organized screening (SIARS)*, n.d.). A total of 13 primary health care units agreed to participate. All health care units implemented steps 1 and 2, and 10 agreed to implement step 3 (Appendix A).

2.2. Randomization and blinding

Clinical secretaries identified all potential participants from the databases used for cancer screening management in each center. The principal investigator generated the randomization sequence, stratified by Health Care Area and primary health care unit and assigned women to the intervention and control groups (World Health Organization, 2017). Participants, the research team and health professionals were not blinded.

2.3. Intervention

The intervention comprised the use of different invitation strategies, organized in three steps and applied sequentially (Fig. 1).

2.3.1. Step 1 – automated and customized text messages, phone calls and reminders

This intervention was based on an invitation to cervical cancer screening through automated and customized text messages and phone calls. An appointment date/time was proposed by text message, and women were asked to confirm their attendance; a reminder message was sent 24–48 h before the date/time of the scheduled appointments. If women were not available, they could ask for a new appointment date/time replying to the invitation text message or phone call. This intervention was described in detail elsewhere (Firmino-Machado et al., 2017; Firmino-Machado et al., 2018).

2.3.2. Step 2 – phone calls performed by clinical secretaries

Women remaining non-adherent to organized cervical cancer screening up to 45 days after step 1 invitations were enrolled in step 2; this comprised an invitation through a phone call performed by a clinical secretary. Clinical secretaries followed a predefined interview script in their contacts (Firmino-Machado et al., 2017). When women did not answer the phone call, a new attempt was performed on the following day, for a maximum of three days. Participants who answered the phone call were invited to cervical cancer screening and an appointment was scheduled for those who agreed to participate, for a date/time convenient for both women and their medical doctor. Those refusing to participate were asked to provide the reason for not adhering to organized screening.

A delay in the implementation of the intervention according to the predefined schedule resulted in 22 participants not receiving the step 2 intervention.

2.3.3. Step 3 – phone calls/face-to-face appointments conducted by medical doctors

Women who remained non-adherent to organized cervical cancer screening, up to 45 days after step 2 invitations, were enrolled in step 3. This comprised a phone call and a face-to-face interview, both performed by a resident medical doctor with at least two years of experience as a family doctor. Physicians followed a predefined interview script in their invitations (Firmino-Machado et al., 2017). When the phone call was not answered, a new attempt was performed on the next day, for a maximum of three days. Women who answered the phone call were invited for a face-to-face appointment to discuss cervical cancer screening, scheduled for a date/time convenient for both women and their medical doctor. During the face-to-face interviews, physicians described screening using a pamphlet, which contains details about how the cytology is performed and answers to the most frequently asked questions. Additionally, medical doctors identified and tried to

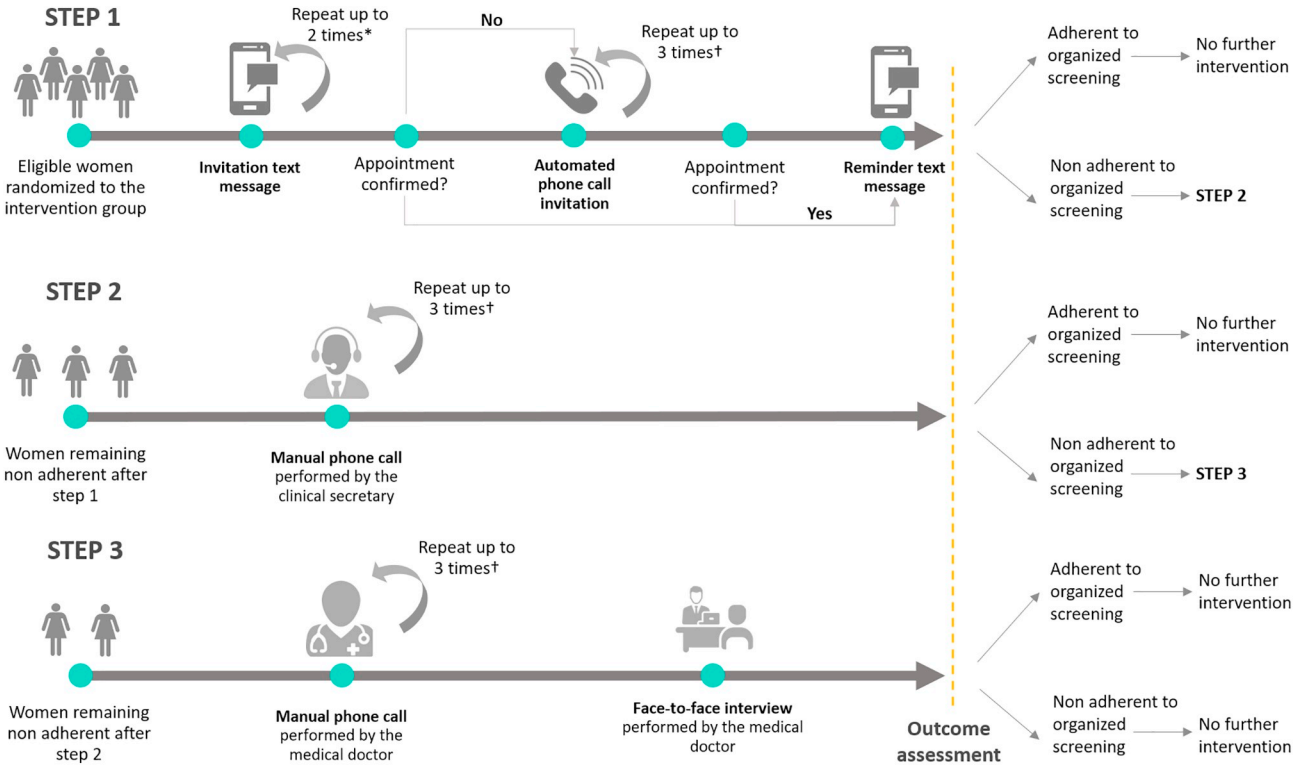

Fig. 1. Description of the intervention.
*When a text message was not delivered successfully a new attempt was performed on the following day. †When a connection was not established, a new phone call was performed on the following day, for a maximum of three days.

overcome any motive perceived by the participants for not undergoing cervical cancer screening, using a prespecified list of arguments (Firmino-Machado et al., 2017). At the end of the appointment, women were invited for screening, on the same day or on another day, at the participants' convenience. Those refusing a face-to-face interview or participation in organized screening were asked to provide the reason for not adhering.

Three of the participant primary care units could not participate in step 3 because there were no medical doctors available to implement the intervention; as a result, 113 women from these units did not undergo step 3 intervention.

2.4. Control

Women in the control group were invited to cervical cancer screening through a written letter, which corresponds to the standard of care. The invitation letter was personalised with women's first and last names, name of the primary care unit and physician's name. It predefined a date/time for the appointment and was sent 45 days before the proposed date; however, women could reschedule the proposed date/time using a phone number provided in the written letter, or in person at their primary care unit (Fig. 2).

No further invitations were issued, during the study period, when women did not adhere to cervical cancer screening or the letter was returned by the post-office services (Fig. 1).

2.5. Outcomes

We tested the superiority of the interventions based on step 1, steps 1 + 2 and steps 1 + 2 + 3, as the primary objective, and the superiority of step 2 and step 3 interventions, as secondary objectives. Fig. 2 describes the timings considered to implement the intervention and the control, as well as the outcome assessment timepoints. The calculation of study outcomes is described in Appendix B.

The clinical records of each participant were searched by medical doctors not involved in providing care to these women, for assessment of the following outcomes:

cumulative proportion of women screened after step 1, steps 1 + 2 and steps 1 + 2 + 3;
proportion of women screened after step 2 and after step 3.

In both intervention and control groups, adherence to cervical cancer screening was determined 45, 90 and 150 days after the initial invitation, for step 1, step 2 and step 3, respectively.

2.6. Sample size

The sample size needed to address the primary objectives of this study was determined assuming a significance level of 5%, a statistical power of 90% and a 1:1 allocation of participants to intervention and control groups. Assuming an adherence proportion in the intervention and control groups of 50% (Baron et al., 2008) and 40%, respectively, after step 1, 60% (Eaker et al., 2004; Vogt et al., 2003) and 45%, respectively, after steps 1 + 2, and 70% (Firmino-Machado et al., 2017) and 50%, respectively, after steps 1 + 2 + 3, the estimated overall sample size was 1038 for step 1, 488 for steps 1 + 2 and 268 for steps 1 + 2 + 3. Therefore, the overall sample size was determined by the step 1 intervention and corresponds to a total of 1038 participants. Since the outcomes considered for the three primary objectives are not independent, no correction for multiple comparisons was made. The isolate effects of step 2 and step 3 were defined as secondary objectives and, as such, not considered when defining the sample size.

2.7. Statistical analysis

The primary strategy of data analysis was based on intention-to-treat (ITT); there were no losses to follow-up and all participants

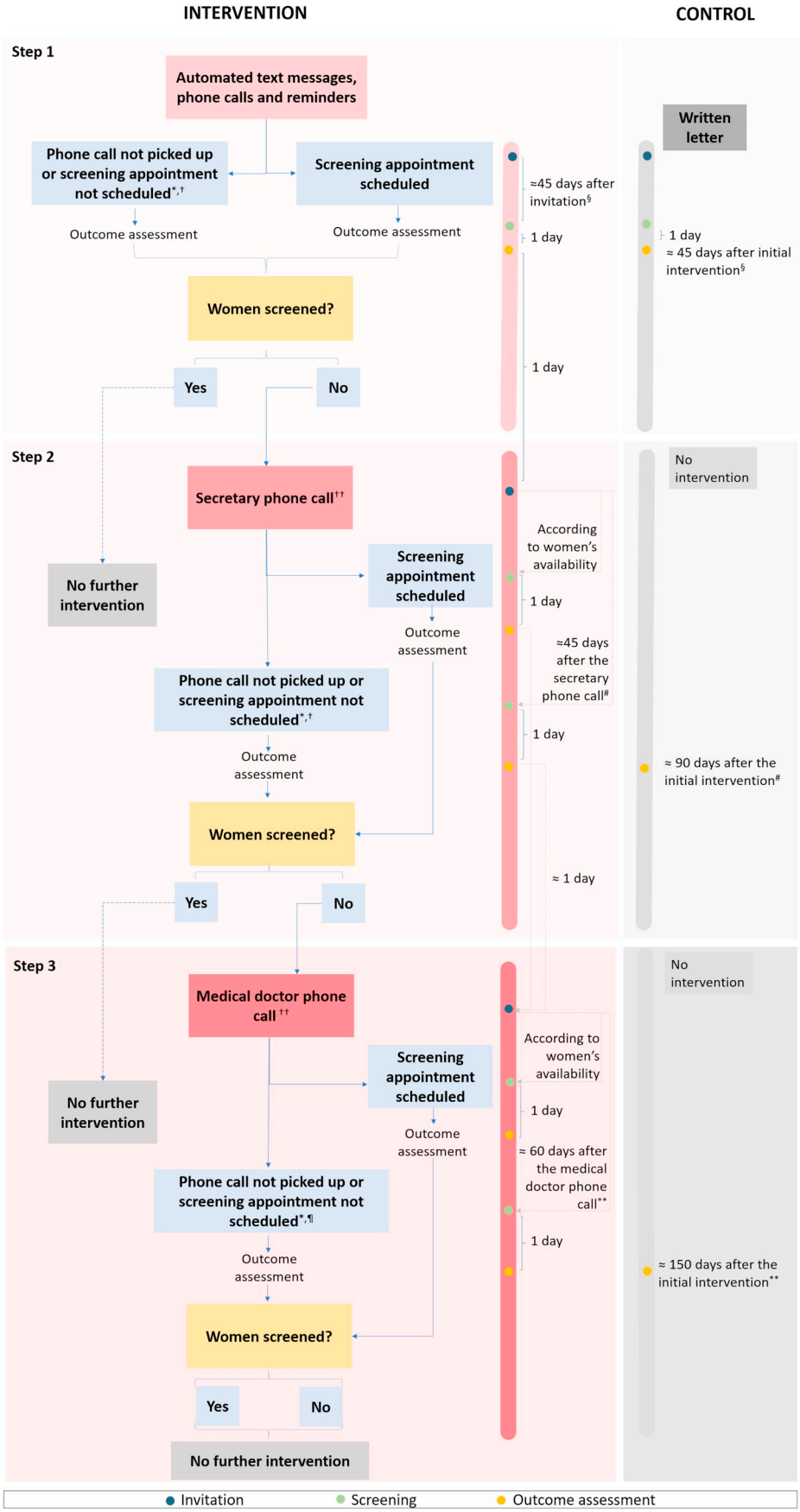

Fig. 2. Implementation of the intervention, timing of invitation for cervical cancer screening and index dates for outcome assessment.
*Women not scheduling a screening appointment within the screening program could undergo opportunistic screening. †Women were asked to provide the reason for not scheduling the appointment after the secretary phone call. ††When the connection was not established, a new phone call was performed on the following day, for a maximum of three days. ¶Women were asked to provide the reason for not scheduling the appointment after a medical doctor phone call. §The index date for outcome assessment was the day after the scheduled appointment (initially proposed or after rescheduling asked by the women). #The assessment date was adjusted (may be less or over 45 days) according to the median time between the invitation phone call performed by the secretaries and the date of the scheduled appointment, for the participants in the same primary care unit. **The assessment date was adjusted (may be less or over 60 days) according to the median time between the invitation phone call performed by the medical doctor and the date of the scheduled appointment, for the participants in the same primary care unit.

Table 1
Characteristics of the participants at the beginning of step 1 (baseline), step 2 and step 3.

	Step 1[a] (n = 1220)		Step 2[a] (n = 853)		Step 3[a] (n = 737)	
	Intervention (n = 605)	Control (n = 615)	Intervention (n = 369)	Control (n = 457)	Intervention (n = 311)	Control (n = 426)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)						
25–34	307 (50.7)	319 (51.9)	202 (54.7)	236 (51.6)	172 (55.3)	216 (50.7)
35–49	298 (49.3)	296 (48.1)	167 (45.3)	221 (48.4)	139 (44.7)	210 (49.3)
Education (years)[b]						
< 9	30 (10.1)	32 (10.6)	15 (9.1)	19 (9.1)	13 (9.8)	18 (9.4)
9–11	40 (13.4)	50 (16.5)	20 (12.2)	34 (16.3)	16 (12.0)	30 (15.6)
12	59 (19.8)	71 (23.4)	31 (18.9)	50 (23.9)	27 (20.3)	46 (24.0)
> 12	169 (56.7)	150 (49.5)	98 (59.8)	106 (50.7)	77 (57.9)	98 (51.0)
Household size (number of people including the participant)						
1 or 2	301 (49.8)	322 (52.4)	193 (52.3)	245 (53.6)	166 (53.4)	229 (53.8)
> 2	304 (50.2)	293 (47.6)	176 (47.7)	212 (46.4)	145 (46.6)	197 (46.2)
Employment status[c]						
Student	23 (4.1)	29 (5.1)	20 (5.8)	23 (5.5)	16 (5.6)	21 (5.3)
Employed	423 (75.0)	393 (68.7)	255 (74.6)	291 (69.1)	209 (73.6)	272 (69.1)
Unemployed	110 (19.5)	141 (24.7)	61 (17.8)	101 (24.0)	55 (19.4)	95 (24.1)
Retired	8 (1.4)	9 (1.6)	6 (1.8)	6 (1.4)	4 (1.4)	6 (1.5)
Occupation (among the employed)[d,e]						
Blue collar	52 (22.8)	55 (27.9)	36 (25.9)	22 (18.0)	52 (22.8)	55 (27.9)
White collar	176 (77.2)	142 (72.1)	103 (74.1)	100 (82.0)	176 (77.2)	142 (72.1)
Health care area						
Porto Ocidental	445 (73.6)	468 (76.1)	264 (71.5)	347 (75.9)	221 (71.1)	320 (75.1)
Marão e Douro Norte	160 (26.4)	147 (23.9)	105 (28.5)	110 (24.1)	90 (28.9)	106 (24.9)
Deprivation index of the place of residence[f,g]						
≤ −1.774 (least deprived)	221 (36.8)	240 (39.1)	136 (37.3)	180 (39.5)	112 (36.5)	170 (40.0)
−1.773 to −0.605	70 (11.6)	81 (13.2)	43 (11.8)	60 (13.2)	33 (10.7)	54 (12.7)
−0.606 to 0.338	86 (14.3)	82 (13.3)	53 (14.5)	64 (14.0)	50 (16.3)	62 (14.6)
0.339 to 1.581	83 (13.8)	86 (14.0)	60 (16.4)	64 (14.0)	51 (16.6)	58 (13.6)
≥1.582 (most deprived)	141 (23.5)	125 (20.4)	73 (20.0)	88 (19.3)	61 (19.9)	81 (19.1)
Previous participation in organized screening and frequency of attendance[h]						
Never attended	210 (34.7)	233 (37.9)	162 (43.9)	192 (42.0)	145 (46.6)	184 (43.2)
Attended irregularly	276 (45.6)	260 (42.3)	155 (42.0)	190 (41.6)	126 (40.5)	176 (41.3)
Attended regularly	119(19.7)	112 (19.8)	52 (14.1)	75 (16.4)	40 (12.9)	66 (15.5)

[a] No statistically significant differences between intervention and control groups were observed for any characteristic.
[b] Data on education is missing for 619 (baseline), 453 (step 2) and 412 (step 3) participants.
[c] Data on employment status is missing for 83 (baseline), 63 (step 2) and 59 (step 3) participants.
[d] Data on occupation is missing for 392 (baseline), 285 (step 2) and 56 (step 3) participants.
[e] According to the International Standard Classification of Occupation.
[f] Deprivation index could not be computed for participants who had place of residence outside Portugal.
[g] The Portuguese version of the European Deprivation Index was used to classify the place of residence of each participant, using the quintiles of the distribution in Portugal as cut-offs (it ranged from −6.6 to 14.7 in the intervention group and from −6.8 to 8.9 in the control group) (Ribeiro et al., 2017).
[h] Adherence to the three previous screening rounds of organized cervical cancer screening was classified as regular attendance.

randomized were considered for the ITT analyses, regardless of being registered in primary care units that did not implement all steps of the intervention. Additionally, per-protocol (PP) analyses were conducted to estimate the efficacy of step 1, step 2, step 3, step 1 + 2 and step 1 + 2 + 3 interventions, including only the participants who fulfilled all of the following criteria: a) women with no exclusion criteria identified after randomization; b) women invited to screening as defined in the protocol for each step or sequence of steps of the intervention; c) women who received the screening invitation, i.e., phone number not reported as invalid or letter not returned, as applicable.

The chi-squared test was used to test differences in women's characteristics and adherence proportions between the intervention and control groups. Binary logistic regression models were used to adjust for expected differences in women's characteristics between the intervention and control groups in the PP analyses, but also to control for residual confounding in the ITT analyses. Confounders were previously defined in the study protocol.

Stratified analyses were conducted, to assess the heterogeneity in the effects of the intervention across subgroups of participants defined according to age, Health Care Area, deprivation of the place of residence and previous participation and frequency of attendance in organized screening. The latter was defined using the Portuguese version of the European Deprivation Index (Ribeiro et al., 2017).

All tests were two-tailed, with a p-value of 0.05 indicating statistical significance.

3. Results

A total of 1220 women were randomized, 605 to the intervention and 615 to the control. The mean age of the participants was 34.0 years (standard deviation (SD) = 7.9) and 35.2 years (SD = 7.4) in the intervention and control groups, respectively. Women's sociodemographic characteristics and previous adherence to cervical cancer screening were similar between groups at baseline, step 2 and step 3 (Table 1).

3.1. Step 1

In the intervention group, the invitation text message/automated phone call was delivered to 517 (85.5%) women (Fig. 3). In the control group, 609 (99.0%) participants received the written letter. Adherence

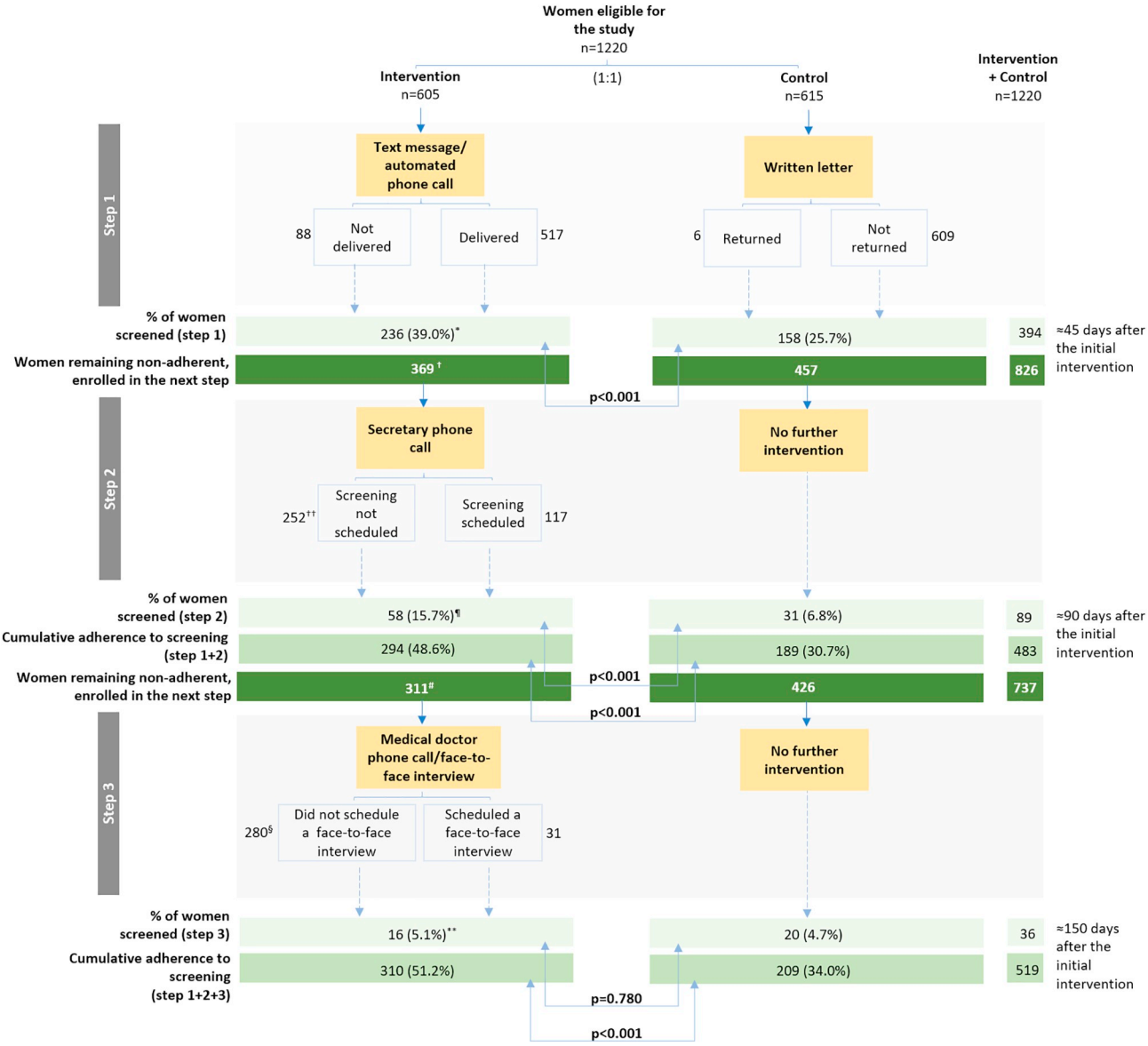

Fig. 3. Delivery of invitations and adherence to screening among intervention and control groups.
*Includes 14 women who were screened despite text messages/automated phone calls were not delivered. †For 31 women an exclusion criterion was identified before implementing step 2: prior cervical cancer (n = 2), hysterectomy (n = 4), no previous sexual relations (n = 2), pregnancy (n = 10), register on a non-participant primary care unit (n = 4), cervical cancer screening was updated before randomization (n = 9). A total of 338 women remained eligible, however only 316 were invited by the clinical secretaries (22 were not invited). ††Includes 130 women to whom a phone call was established and from these 60 (46.2%) answered the call. ¶Includes six women who were screened, despite they had no scheduled appointment. #For 31 women an exclusion criterion was identified before implementing step 3: prior cervical cancer (n = 2), hysterectomy (n = 5), no previous sexual relations (n = 3), pregnancy (n = 7), register on a non-participant primary care unit (n = 4), cervical cancer screening was updated before randomization (n = 10). A total of 280 women remained eligible, however the intervention was not implemented by three of the involved primary care units (corresponds to 114 women), and therefore only 166 women received a medical doctor phone call. §Includes 91 women to whom a phone call was established and from these 53 (58.2%) answered the call. **Includes six women who were screened despite they had no scheduled face-to-face interview or received the medical doctor phone call.

to cervical cancer screening was significantly higher among women in the intervention than in the control group (39.0% vs. 25.7%, $p < 0.001$).

3.2. Step 2

In the intervention group, 369 women remained non-adherent after step 1. Only 316 were invited by the clinical secretaries, because an exclusion criterion was identified for 31 women just before step 2 and the intervention was not implemented to 22 participants, due to administrative errors (Fig. 3). Among the 369 women included in step 2, 48% (177/369) answered the phone call and 32% (117/369) scheduled a screening appointment. The most frequent reasons for not adhering were preference for screening in the private sector (49.2%), and the large distance between the primary care unit and the women's place of residence/work (30.2%) (Appendix C). In the control group, 457 women remained non-adherent after step 1 and they were all included in step 2.

Using an ITT analyses of steps 1 + 2, adherence to cervical cancer screening was significantly higher among women assigned to the intervention (48.6% vs. 30.7%, $p < 0.001$) (Table 2). When this analysis was restricted to step 2, adherence was also significantly higher among women assigned to the intervention than those in the control group (15.7% vs. 6.8%, $p < 0.001$), as depicted in Fig. 3.

Table 2
Intention-to-treat and per-protocol analyses for the comparison between intervention and control groups.

	Intervention		Control		% Difference (95% CI)	p-Value[a]	Crude OR (95% CI)	p-Value	Adjusted[b] OR (95% CI)	p-Value
	n	$n_{screened}$ (% screened)	n	$n_{screened}$ (% screened)						
Intention-to-treat analysis										
Step 1	605	236 (39.9)	615	158 (25.7)	13.3 (8.1 to 18.5)	< 0.001	1.85 (1.45 to 2.36)	< 0.001	1.87 (1.46 to 2.39)	< 0.001
Step 1 + 2	605	294 (48.6)	615	189 (30.7)	17.9 (12.4 to 23.2)	< 0.001	2.13 (1.69 to 2.69)	< 0.001	2.16 (1.71 to 2.74)	< 0.001
Step 1 + 2 + 3	605	310 (51.2)	615	209 (34.0)	17.3 (11.7 to 22.6)	< 0.001	2.04 (1.62 to 2.57)	< 0.001	2.07 (1.64 to 2.63)	< 0.001
Per-protocol analysis[c]										
Step 1	517	222 (42.9)	609	158 (25.9)	17.0 (11.5 to 22.4)	< 0.001	2.14 (1.67 to 2.76)	< 0.001	2.14 (1.66 to 2.77)	< 0.001
Step 2	247	57 (23.1)	441	31 (7.0)	16.1 (10.5 to 20.1)	< 0.001	3.97 (2.48 to 6.35)	< 0.001	4.11 (2.56 to 6.62)	< 0.001
Step 3[d]	119	11 (9.2)	265	7 (2.6)	6.6 (1.8 to 13.3)	0.005	3.75 (1.42 to 9.94)	0.008	3.71 (1.38 to 10.0)	0.009
Step 1 + 2	434	276 (63.6)	593	188 (31.7)	31.9 (25.9 to 37.6)	< 0.001	3.76 (2.89 to 4.89)	< 0.001	3.86 (2.96 to 5.04)	< 0.001
Steps 1 + 2 + 3[d]	273	179 (65.6)	365	121 (33.2)	32.4 (24.8 to 39.5)	< 0.001	3.84 (2.76 to 5.35)	< 0.001	4.13 (2.92 to 5.84)	< 0.001

CI - confidence interval.

[a] Comparison between intervention and control.

[b] Adjusted for age (continuous), education (< 9, 9–12, 12, > 12 years), household size (≤ 2 vs. > 2 people), employment status (student/employed vs. unemployed/retired), occupation (white collar vs. blue collar), Health Care Area (Porto Ocidental vs. Marão e Douro Norte), deprivation index (continuous variable) and previous participation in organized screening (never attended, attended irregularly, attended regularly).

[c] These analyses exclude women who were classified as non-eligible after randomization, those who have an invalid phone number (intervention group) and those with invalid address (control group).

[d] This analysis excludes all the women defined in [c] and those registered at primary care units that did not implement the step 3 intervention.

In the PP analyses (Table 2), adherence was significantly higher in the intervention group when considering step 2 alone (23.1% vs. 7.0%, $p < 0.001$) and after steps 1 + 2 (63.6% vs. 31.7%, $p < 0.001$).

3.3. Step 3

In the intervention group, 311 women remained non-adherent after step 2. Only 166 were invited by the medical doctors, because an exclusion criterion was identified for 31 women just before step 3 and the intervention was not implemented to 114 participants due to difficulties of medical doctors in fitting these activities in their clinical agendas (Fig. 3). Among the 311 women included in step 3, 27% (84/311) answered the phone call and 10% (31/311) scheduled a face-to-face interview. The most frequent reasons for not adhering were preference for screening in the private sector (58.2%) and the large distance between the primary care unit and women's place of residence/work (30.9%) (Appendix C). In the control group, 426 women remained non-adherent after step 2 and they were all included in step 3.

The ITT analysis of the cumulative adherence after steps 1 + 2 + 3 was significantly higher for the women assigned to the intervention group (51.2% vs. 34.0%, $p < 0.001$). When this analysis was restricted to step 3, adherence was not significantly different between women assigned to intervention and control groups (5.1% vs. 4.7%, $p = 0.780$), as depicted in Fig. 3.

In PP analyses (Table 2), the adherence was significantly higher in the intervention group when considering step 3 alone (9.2% vs. 2.6%, $p = 0.005$), and after steps 1 + 2 + 3 (65.6% vs. 33.2%, $p < 0.001$).

3.4. Stratified analyses

The effectiveness of the intervention was lowest among women who never attended organized screening, those living in intermediately deprived areas and those aged 25–34 years, though differences across strata were statistically significant for age (Appendix D). For steps 1 + 2 and steps 1 + 2 + 3 the differences between the intervention and control groups were 9.9% (95% CI 1.8% to 18.0%) and 10.2% (95% CI 1.8% to 18.5%), respectively, among participants not previously adherent to organized screening, 13.1 (95% CI 2.2 to 23.6) and 13.6 (95% CI 2.5 to 24.2), respectively, for participants living in intermediately deprived areas, and 11.7% (95% CI 4.1% to 19.1%) and 11.5% (95% CI 3.8% to 10.1%), respectively, among younger women.

4. Discussion

The SCAN-Cervical Cancer trial showed that women invited for organized cervical cancer screening through a stepwise strategy based on automated text messages/phone calls (step 1), manual phone calls (step 2) and face-to-face interviews (step 3) were more adherent than those invited by written letter.

Notwithstanding, in an ITT analysis the effectiveness did not increase after step 3. This largely reflects that the step 3 was not implemented by three of the enrolled primary care units. The poor adherence after step 3 may also be explained because 60% of the women reported a preference to be screened at the private sector (Appendix C). Additionally, among the women contacted in step 3 who refused to participate nearly 10% reported their house/work place as far from the primary care unit, and just over 20% were living abroad, which precluded participation in screening. If the latter had been excluded before randomization the effectiveness of the interventions may have been greater, but such information was not available in the administrative records.

The large proportion of invalid mobile phone numbers among invited women precluded the delivery of the tested interventions, reducing their effectiveness, as supported by greater effect estimates in the PP analyses. Although, there is potential for the differences between the results from the ITT and PP analyses to be reduced in the near future, since there is an ongoing optimization of the phone number records in Portuguese primary health care units, decisions on the most appropriate strategy for screening invitation should be based primarily on the results of the ITT analyses (Ministry of Health, n.d.).

Medical doctors of three primary health care units did not implement the step 3 intervention because they were not able to include these more demanding tasks in their overloaded schedules. The implementation of this strategy may be improved if new types of appointments are defined for this purpose, but medical doctors may still use these appointments for other tasks, since they often lack time for their clinical activities.

The cumulative effect of an invitation to cervical cancer screening through a written letter was 26% after step 1, 30% after step 2 and 34% after step 3. This increase may be explained by an increasing follow-up time, that allowed participants to reschedule their appointments if they were not previously available for the initially proposed date/time. Additionally, the longer the time-frame for the quantification of the

outcome, the more likely it is that a greater number of women undergoing opportunistic screening are included, as a result of invitations performed by medical doctors during appointments scheduled for other health purposes.

Contamination may have occurred because all participants have access to screening for free and those allocated to the intervention group may live geographically near to those in the control group and influence them. This may have contributed to explain the increase in adherence from step 1 to 3 in the control group, and to dilute the difference between study arms, ultimately resulting in conservative effect estimates.

Participants in the control group received only one written letter (i.e., the standard of care in Portugal), whereas those in the intervention group received up to twelve invitation attempts. Therefore, the effectiveness of the tested intervention is a consequence of both the type of contact method and its' intensity. Further studies are required to clarify if the proposed intervention would remain effective when compared to a more intensive control (e.g., larger number of invitation letters).

The proposed intervention may be also useful to promote adherence to screening in a context other than an organized program. In our study we tested the joint effect of these components under a scenario of systematic invitation. Nevertheless, we may speculate that the more intensive components of the intervention may be more effective among women invited for screening opportunistically, as these are more likely to be regular users of the primary health care services.

Regarding the strata-specific results according to the deprivation of the place of residence, the differences between groups were not statistically significant. This suggests that this invitation strategy may include methods able to reach populations with distinct socio-economic backgrounds.

4.1. Strengths and limitations

To the best of our knowledge, this is one of the first pragmatic randomized controlled trials testing a multistage intervention with increasing complexity to increase adherence to cervical screening. Although it adds a methodologically robust assessment of a comprehensive strategy to promote cancer screening to previous research, there are some limitations that deserve discussion.

The exclusion of potentially eligible women because no mobile phone number was available is expected to have a small impact in the validity of the study, since they correspond to < 3% of the overall number of participants.

Although cervical cancer screening is recommended for women aged 25–65 years, we have included only those aged below 50 years, because the intervention required the use of mobile phone and the proportion of users is higher in the younger women (Portuguese National Institute of Statistics (Instituto Nacional de Estatística), n.d.). This is not expected to have an impact on the internal validity, although this restriction in the selection criteria precludes the generalization of the conclusions to older women.

5. Conclusion

This trial showed that a stepwise invitation to cervical cancer screening based on automated strategies, manual phone calls and face-to-face interviews is significantly more effective than the standard of care; in this setting it is expected to increase adherence to cervical cancer screening by at least 17%. The tested intervention has the potential to be broadly implemented due to the low requirements of technology and health professionals training.

Ethics approval and consent to participate

Approved by the Portuguese regional ethics committee – Comissão de Ética da Administração Regional de Saúde do Norte (number: 20/2017) and by the National Data Protection Committee (number: 11467/2016). The trial was registered with the name “Stepwise Strategy to Improve Cervical Cancer Screening Adherence (SCANCC): Automatic Text Messages, Phone Calls and Face-to-face Interviews” and assigned the number NCT03122275 (ClinicalTrial.Gov). No informed consent was considered due to the nature of the intervention to be tested. The harms of the intervention are largely outweighed by its benefits, as supported by the ethics committee who reviewed the research project.

Conflict of interest

All the authors declare that they have no financial nor non-financial competing interests.

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Authors' contributions

JFM and NL designed the study. JFM, RM, AM enrolled the recruiting sites, family doctors and clinical secretaries in the study. SCANCC collaborators recruited the study participants and verified their eligibility. JFM and SV collected the study and study variables from the medical records. JFM conducted the data analysis and drafted the first version of the manuscript with contributions of NL. JFM and NL edited the draft of the manuscript. All authors and collaborators revised and approved the final version of the manuscript.

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SCAN-Cervical Cancer collaborators:

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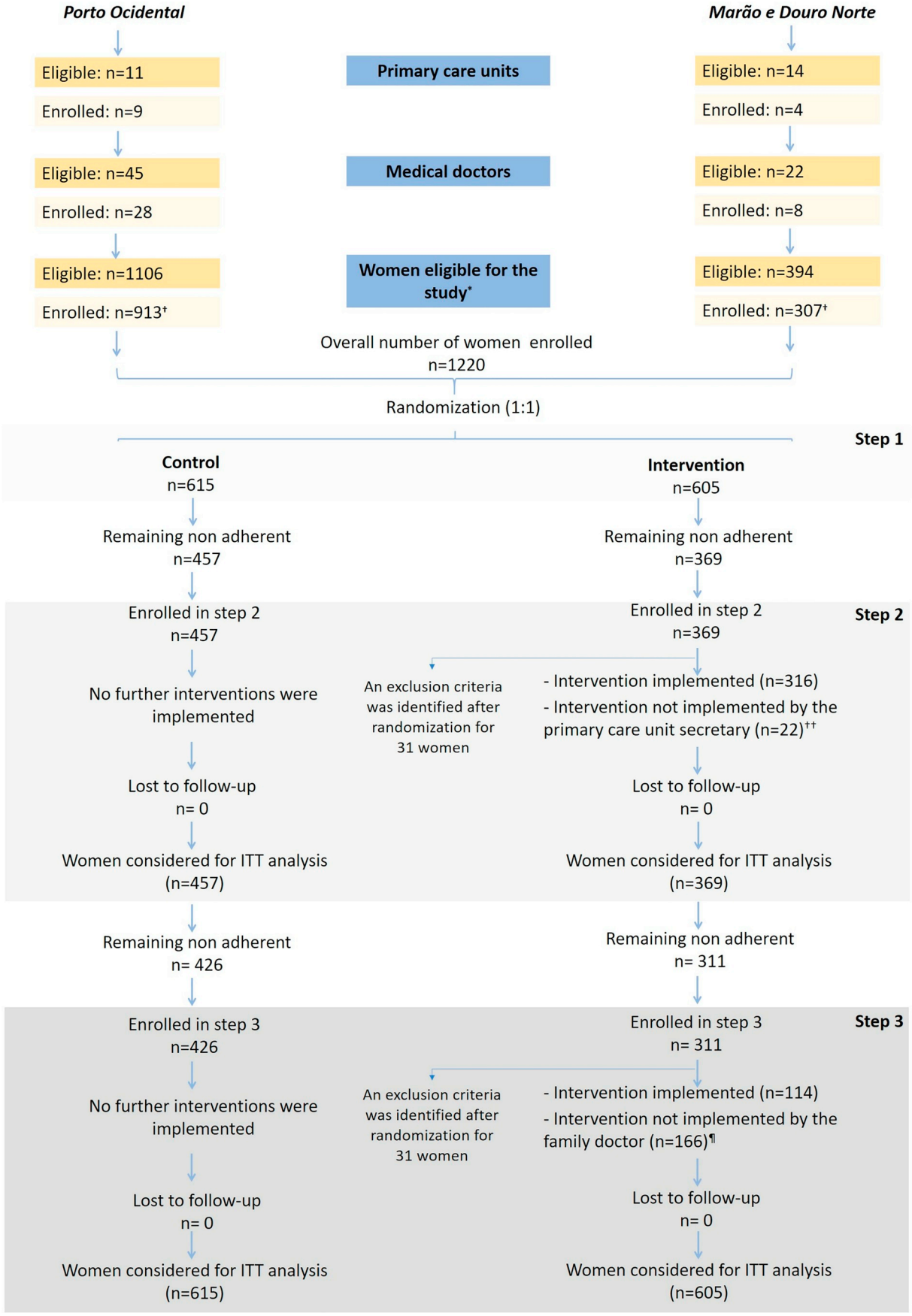
Appendix A. Enrolment, allocation and follow-up of participants



*Women aged 25 to 49 years, eligible for cervical cancer screening and registered at primary care units from *Porto Ocidental* or *Marão e Douro Norte* that systematically invite women to be screened through a written letter; a total of 27 women (11 from Porto Ocidental and 16 from Marão e Douro Norte) were excluded before randomization, because they had no mobile phone number registered at the National Health Service database. †Physicians did not have enough time to implement the intervention to all the eligible women and therefore, only a subgroup of randomly selected eligible women was enrolled. ††A delay in the implementation of the intervention according to the predefined schedule (Fig. 2) resulted in 22 participants not receiving the step 2 intervention. ¶The intervention was not implemented in three primary care units, what corresponds to 113 of the women enrolled in step 3.

Appendix B. Definition and index dates for outcome assessment and calculation of outcome measures

		Outcome	Index date for outcome assessment: Women with a scheduled screening appointment	Index date for outcome assessment: Women with no scheduled screening appointment	Calculation	
Intervention	Intention-to-treat	Adherence to screening **after step 1**	Day after appointment	45 days after sending the text messages/phone calls	*Numerator*	Number of women screened after step 1
					Denominator	Number of women assigned to the intervention group
		Adherence to screening **after steps 1+2** interventions	Day after appointment	90 days after sending the text messages/phone calls	*Numerator*	Number of women screened after step 1+2
					Denominator	Number of women assigned to the intervention group
		Adherence to screening **after steps 1+2+3** interventions	Day after appointment	150 days after sending the text messages/phone calls	*Numerator*	Number of women screened after step 1+2+3
					Denominator	Number of women assigned to the intervention group
	Per-protocol	Adherence to screening **after step 2** intervention	Day after appointment	45 days after secretary phone call (corresponds to 90 days after sending text messages/phone calls)	*Numerator*	Number of women screened after step 2, among those remaining non-adherent after step 1
					Denominator	Number of women assigned to the intervention group and enrolled in step 2, with a valid phone number, to whom step 2 intervention was implemented and with no exclusion criteria identified after randomization
		Adherence to screening **after step 3** intervention	Day after appointment	60 days after medical doctor's face-to-face interview (corresponds to 150 days after sending text messages/phone calls)	*Numerator*	Number of women screened after step 3, among those remaining non-adherent after step 2
					Denominator	Number of women assigned to the intervention group and enrolled in step 3, with a valid phone number, to whom step 2 intervention was implemented and with no exclusion criteria identified after randomization
Control	Intention-to-treat	Adherence to screening after written letter (**step 1**)	45 days after sending the written letter		*Numerator*	Number of women screened after step 1
					Denominator	Number of women assigned to the control group
		Adherence to screening after written letter (**steps 1+2**)	90 days after sending the written letter		*Numerator*	Number of women screened after step 1+2
					Denominator	Number of women assigned to the control group
		Adherence to screening after written letter (**steps 1+2+3**)	150 days after sending the written letter		*Numerator*	Number of women screened after step 1+2+3
					Denominator	Number of women assigned to the control group
	Per-protocol	Adherence to screening after written letter (**step 2**)	90 days after sending the written letter		*Numerator*	Number of women screened after step 2, among those remaining non-adherent after step 1
					Denominator	Number of women assigned to the control group and enrolled in step 2, with a valid adress
		Adherence to screening after written letter (**step 3**)	150 days after sending the written letter		*Numerator*	Number of women screened after step 3, among those remaining non-adherent after step 2
					Denominator	Number of women assigned to the control group and enrolled in step 3, with a valid adress

Appendix C. Reasons for not scheduling a screening appointment

Reasons for not adhering to organized screening (among women who picked up the phone call performed by the secretary/medical doctor	Step 2 (n=113) n (%)	Step 3 (n=104) n (%)	Steps 2 or 3 (n=146) n (%)*
Screened at the private sector	31 (49.2)	32 (58.2)	44 (62.0)
Intends to be screened at her primary care unit	0 (0.0)	3 (5.5)	3 (4.2)
Intends to be screened at the private sector	31 (49.2)	29 (52.7)	41 (57.8)
Far from the primary care unit	19 (30.2)	17 (30.9)	21 (29.6)
Living in the country, but far from the primary care unit where is registered	5 (7.9)	6 (10.9)	6 (8.5)
Living in a different country	14 (22.3)	11 (20.0)	15 (21.1)
Agenda restrictions	4 (6.3)	5 (9.1)	6 (8.5)
Refuses to undergo screening	7 (11.1)	0 (0.0)	7 (9.9)
Wants to be screened by another medical doctor	1 (1.6)	0 (0.0)	1 (1.4)
Uncertain about the benefits of screening	1 (1.6)	1 (1.8)	2 (2.8)
No motive was given, when asked	0 (0.0)	0 (0.0)	0 (0.0)
Motive was not registered by the health professional	0 (0.0)	0 (0.0)	0 (0.0)

Appendix D. Stratified intention-to-treat analysis of the effect of steps 1 + 2 and steps 1 + 2 + 3

	Intervention		Control		% Difference (95% CI)	p-value*	Crude OR (95% CI)	Adjusted† OR (95% CI)	p-value for the interaction††
	n	$n_{adherent}$ (% adherence)	n	$n_{adherent}$ (% adherence)					
Intention-to-treat analysis of adherence									
All women - step 1+2[§]									
Age (years)									0.027
25-34	307	135 (44.0)	319	103 (32.3)	11.7 (4.1 to 19.1)	0.003	1.65 (1.19 to 2.28)	1.67 (1.20 to 2.32)	
35-49	298	159 (53.4)	296	86 (29.1)	24.3 (16.5 to 31.7)	<0.001	3.85 (1.85 to 7.98)	2.85 (2.02 to 4.03)	
Health Care Area									0.758
Porto Ocidental	445	224 (50.3)	468	148 (31.6)	18.7 (12.4 to 24.9)	<0.001	2.19 (1.67 to 2.87)	2.20 (1.67 to 2.89)	
Marão e Douro Norte	160	70 (43.8)	147	41 (27.9)	15.9 (5.1 to 26.0)	0.004	2.01 (1.25 to 3.24)	2.07 (1.27 to 3.37)	
Deprivation of the place of residence[¶]									0.726
Least deprived	262	128 (48.9)	295	85 (28.8)	20.0 (12.0 to 27.8)	<0.001	2.36 (1.66 to 3.35)	2.29 (1.61 to 3.27)	
Intermediately deprived	153	65 (42.5)	143	42 (29.4)	13.1 (2.2 to 23.6)	0.019	1.78 (1.10 to 2.88)	1.78 (1.09 to 2.89)	
Most deprived	186	101 (54.3)	176	62 (35.2)	19.1 (8.8 to 28.7)	<0.001	2.19 (1.43 to 3.34)	2.32 (1.49 to 3.62)	
Previous participation in organized screening and frequency of attendance									0.254
Never attended	210	65 (31.0)	233	49 (21.0)	9.9 (1.8 to 18.0)	0.017	1.68 (1.10 to 2.59)	1.64 (1.05 to 2.54)	
Attended irregularly	276	150 (54.3)	260	84 (32.3)	22.0 (13.7 to 29.9)	<0.001	2.49 (1.76 to 3.55)	2.56 (1.80 to 3.67)	
Attended regularly	119	79 (66.4)	122	56 (45.9)	20.5 (8.0 to 32.1)	0.001	2.33 (1.38 to 3.92)	2.40 (1.39 to 4.12)	
All women - steps 1+2+3[§]									
Age (years)									0.037
25-34	307	146 (47.6)	319	115 (36.1)	11.5 (3.8 to 10.1)	0.004	1.61 (1.17 to 2.22)	1.63 (1.17 to 2.26)	
35-49	298	164 (55.0)	296	94 (31.8)	23.3 (15.4 to 30.8)	<0.001	2.63 (1.88 to 3.68)	2.71 (1.93 to 3.81)	
Health Care Area									0.594
Porto Ocidental	445	237 (53.3)	468	163 (34.8)	18.4 (12.0 to 24.6)	<0.001	2.13 (1.63 to 2.78)	2.14 (1.63 to 2.81)	
Marão e Douro Norte	160	73 (45.6)	147	46 (31.3)	14.3 (3.4 to 24.7)	0.010	1.84 (1.16 to 2.94)	1.88 (1.17 to 3.03)	
Deprivation of the place of residence[¶]									0.516
Least deprived	262	135 (51.5)	295	93 (31.5)	20.0 (11.8 to 27.8)	<0.001	2.31 (1.64 to 3.26)	2.25 (1.58 to 3.20)	
Intermediately deprived	153	69 (45.1)	143	45 (31.5)	13.6 (2.5 to 24.2)	0.016	1.79 (1.11 to 2.78)	1.79 (1.11 to 2.89)	
Most deprived	186	106 (57.0)	176	71 (40.3)	16.7 (6.4 to 26.5)	0.002	1.96 (1.29 to 3.00)	2.05 (1.33 to 3.18)	
Previous participation in organized screening and frequency of attendance									0.366
Never attended	210	71 (33.8)	233	55 (23.6)	10.2 (1.8 to 18.5)	0.017	1.65 (1.09 to 2.51)	1.61 (1.05 to 2.46)	
Attended irregularly	276	156 (56.5)	260	90 (34.5)	21.9 (13.5 to 29.9)	<0.001	2.46 (1.73 to 3.48)	2.57 (1.80 to 3.67)	
Attended regularly	119	83 (69.7)	122	64 (52.5)	17.3 (5.0 to 28.9)	0.006	2.09 (1.23 to 3.54)	2.10 (1.21 to 3.65)	

CI - Confidence Interval. [a]Comparison between intervention and control. [b]Adjusted for age (continuous), education (< 9, 9–12,12, > 12 years), household size (≤2 vs. > 2 people), employment status (student/employed vs. unemployed/retired), occupation (white collar vs. blue collar), Health Care Area (Porto Ocidental vs. Marão e Douro Norte), deprivation index (continuous variable) and previous participation in organized screening (never attended, attended irregularly, attended regularly). [c]p-Value for the interaction between participants' baseline characteristics and the effect of the intervention. [d]Step 1 is an invitation based on automated text messages, phone calls and reminders; step 2 is an invitation based on manual phone calls; step 3 is an invitation based on medical doctors' phone calls and face-to-face interviews. [e]Deprivation index could not be computed for five participants who had place of residence outside Portugal.

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