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Reshaping organized cervical cancer screening: strategies to increase the adherence and reduce invitation costs

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Tese de Doutoramento em Saúde Pública

Porto | 2019

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Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade do Porto

Porto | 2019

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Ao abrigo do Art.º 4º do Decreto-Lei n.º 707/2018, fazem parte desta dissertação as seguintes publicações e manuscritos submetidos para publicação:

I. Firmino-Machado J, Mendes R, Moreira A, Lunet N. 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. BMJ Open. 2017;7:e017730.

II. Firmino-Machado J, Vilela S, Mendes R, Moreira A, Lunet N. Stepwise strategy to improve cervical cancer screening adherence (SCAN-Cervical Cancer) – Automated text messages, phone calls and reminders: population based randomized controlled trial. Prev Med. 2018;114:123–33.

III. Firmino-Machado J, Mendes R, Moreira A, Lunet N. Translating evidence into practice: insights on the reporting of trial results to health professionals and institutions (submitted).

IV. Firmino-Machado J, Varela S, Mendes R, Moreira A, Lunet N. A 3-step intervention to improve adherence to cervical cancer screening: the SCAN randomized controlled trial. Prev Med. 2019;123:250-261.

V. Firmino-Machado J, Soeteman D, Lunet N. Cost-effectiveness of a stepwise intervention to promote adherence to cervical cancer screening (submitted).

Declaro que colaborei ativamente no desenho dos estudos e definição dos objetivos de todos os trabalhos que compõem a presente tese. Fui responsável pela recolha de dados e análise estatística. Colaborei ativamente na interpretação dos resultados e redigi as versões iniciais dos manuscritos.

Esta investigação foi realizada no Instituto de Saúde Pública da Universidade do Porto, sob a orientação do Professor Doutor Nuno Lunet (Faculdade de Medicina da Universidade do Porto e Instituto de Saúde Púbica da Universidade do Porto).

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O alerta da sociedade que (não) queremos,

a reflexão de qual o rumo do conhecimento.

GUERRA É PAZ

LIBERDADE É ESCRAVIDÃO

IGNORÂNCIA É PODER

(1984, George Orwell)

AGRADECIMENTOS

Ao mentor e amigo, Professor Nuno Lunet, a quem devo a capacidade de perguntar e o cientista que sou;

A todos os médicos, enfermeiros e secretários clínicos que estiveram envolvidos neste projeto e, em particular, aos investigadores Sofia Varela, Romeu Mendes, Amélia Moreira e Djøra Soeteman;

Aos meus pais pelo seu infinito amor;

À Isabel pela vida que partilha comigo;

Aos meus amigos, que sempre foram família;

Ao NEMUM, onde aprendi a ser cidadão;

A vós, obrigado.

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ABSTRACT

The sustainability of health systems is being challenged by the increasing demand of financial resources to support pharmacological and diagnostic innovation. Therefore, to ensure long-term universal access to care, an investment shift towards health promotion and disease prevention is required, along with a more efficient management of the scarce financial resources.

Oncologic diseases are among the main causes of morbidity and mortality, particularly in high-income countries, accounting for an expenditure of 1.5% of the world's gross domestic product. However, the number of cancer cases can be reduced substantially through the implementation of prevention and control strategies, such as lifestyle changes, vaccination and screening. Cervical cancer is one of the most preventable oncologic diseases, both through well-organized screening programs and human papillomavirus (HPV) vaccination; nevertheless, it remains the fourth most commonly diagnosed cancer in women globally. Although HPV vaccination may be the most relevant intervention to prevent cervical cancer in the future, organized screening will remain necessary, at least for nonvaccinated women. The simultaneous implementation of these two strategies may compromise the financial sustainability of organized screening, since HPV vaccination will increase the number of women who need to be screened to prevent a cancer death, while the costs with quality assurance and monitoring of organized screening will remain constant. Additionally, population adherence to organized screening is often low, contributing to the inefficient use of the scarce financial resources. Therefore, organized cervical cancer screening needs to be reshaped to ensure its cost-effectiveness, namely through the implementation of strategies that increase women's participation at an affordable price. This may be achieved through the combination of automated and low-cost invitations to cervical cancer screening applied to the entire population, with the remaining non-adherent women receiving more customized and costly interventions.

This thesis intends to test the effectiveness and cost-effectiveness of an invitation strategy, with an increasing level of customization and cost, to increase adherence to organized cervical cancer screening, in comparison with a written letter (*i.e.*, the standard of care). The intervention tested includes automated text messages/phone calls/reminders (step 1), manual phone calls performed by clinical secretaries (step 2) and face-to-face interviews conducted by family doctors (step 3), applied sequentially to women remaining non-adherent after each step.
The following paragraphs describe the specific objectives defined for this thesis, along with the corresponding methods and main results:

1) *To test the superiority of an invitation strategy based on step 1, steps 1+2 and steps 1+2+3 in relation to the standard of care.*

This was accomplished through a multicentre, parallel, population-based randomized controlled trial (*Stepwise Strategy to improve Cervical Cancer Screening Adherence - SCAN trial*), including women eligible for cervical cancer screening, aged 25 to 49 years, registered in the *Porto Ocidental* or *Marão e Douro Norte* Health Care Areas (Portugal), with an available mobile phone number. In the intervention group, women were invited through a stepwise strategy, based on steps 1 to 3, which were applied sequentially to women remaining non-adherent after each step. Women in the control group were invited through a written letter. The primary outcome was the proportion of women screened after step 1 (assessed 45 days after the initial invitation), steps 1+2 (assessed 90 days after the initial invitation) and steps 1+2+3 (assessed 150 days after the initial invitation).

Adherence to cervical cancer screening was significantly higher among women assigned to the intervention, after 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).

To promote the diffusion of this knowledge, the results of step 1 intervention were communicated to the primary health care units and professionals involved in SCAN trial through reports customized according to the primary health care unit characteristics and interests.

2) *To compare the cost-effectiveness of an invitation based on step 1, steps 1+2 and steps 1+2+3 with the standard of care strategy.*

The second objective was addressed through a decision tree model, which compared the cost-effectiveness of four competing invitation strategies to cervical cancer screening: (a) a written letter; (b) step 1 invitation strategy; (c) steps 1+2 invitation strategies; (d) steps 1+2+3 invitation strategies. The main outcome was the cost per quality-adjusted life year (QALY) measured over a five-year time horizon. Adherence to cervical cancer screening after each of the competing interventions was obtained from the SCAN trial and the corresponding QALYs were estimated based on previous studies. Costs were estimated from the provider and societal perspective using patient-level data from the SCAN trial, or if not available, from portuguese data sources or the international literature. The benefits and costs of the invitation strategies were used to compute incremental cost-effectiveness ratios (ICER), which were compared to a willingness-to-pay threshold of €22398 per QALY (*i.e.*, one time the Portuguese gross domestic product per capita). The strategy with the highest ICER just below the threshold was considered the most cost-effective option.

This study showed that an invitation to cervical cancer screening based on steps 1+2 was a very cost-effective strategy (ICER of €4286 and €9394 from the provider and societal perspective, respectively) surpassing the standard of care, which was strongly dominated (*i.e.*, less effective and more costly than other strategies), as well as the interventions based on step 1 or steps 1+2+3.

In conclusion, the results of this thesis show that an invitation strategy with an increasing level of customization, based on automated text messages/phone calls/reminders, manual phone calls and face-to-face interviews or combinations of its' components increased the adherence to organized cervical cancer screening, in comparison with the standard of care. Further, it supports the implementation of automated text messages/phone calls/reminders and manual phone calls as the new standard of care invitation to cervical cancer screening, under a willingness-to-pay threshold of one time the Portuguese gross domestic product per capita.

RESUMO

A sustentabilidade dos sistemas de saúde encontra-se ameaçada pela necessidade crescente de recursos financeiros que suportem a implementação das necessárias inovações ao nível diagnóstico e farmacológico. Assim, para garantir que a longo prazo o acesso aos cuidados de saúde permanece universal, é necessário priorizar o investimento nas áreas de promoção da saúde e prevenção da doença, bem como promover uma gestão mais eficiente do escasso orçamento disponível.

As doenças oncológicas são uma das principais causas de morbilidade e mortalidade, particularmente nos países de mais alto rendimento, sendo os gastos anuais necessários para o seu tratamento superiores a 1,5% do produto interno bruto mundial. No entanto, é possível reduzir de forma substancial o número de novos casos de cancro através da implementação de estratégias de prevenção e controlo, tais como alterações dos estilos de vida, vacinação e rastreio. O cancro do colo do útero é umas das doenças oncológicas mais preveníveis, seja através da administração da vacina do vírus do papiloma humano (HPV) ou do rastreio, apesar de permanecer como a quarta causa mais frequente de cancro nas mulheres, em todo o mundo. No futuro, é expectável que a vacina do HPV se torne a intervenção mais relevante em termos de prevenção do cancro do colo do útero, apesar de continuar a ser necessário a implementação de um rastreio organizado, pelo menos para as mulheres não vacinadas. Contudo, a implementação simultânea destas duas estratégias pode comprometer a sustentabilidade financeira dos programas de rastreio; a vacinação irá aumentar o número de mulheres a rastrear para prevenir uma morte por cancro do colo do útero, mantendo-se, no entanto, os custos com a monitorização e avaliação do rastreio organizado. Além disso, a adesão ao rastreio organizado é frequentemente baixa, contribuindo para a utilização ineficiente dos escassos recursos financeiros do sector da saúde. Desta forma, o rastreio organizado deve ser redesenhado de forma a garantir a sua custo-efetividade, nomeadamente através da implementação de estratégias de custo reduzido que aumentem a participação das mulheres elegíveis. Este objetivo poderá ser alcançado através da utilização de convites automáticos e de baixo custo remetidos para toda a população-alvo e, intervenções mais personalizadas e com maior custo de implementação, para as mulheres que não adiram ao rastreio após esta estratégia.

Esta tese pretende testar a efetividade e custo-efetividade de uma estratégia de convite, com um grau crescente de personalização e custo, para aumentar a adesão ao rastreio organizado do cancro do colo do útero, em comparação com o procedimento de convite habitualmente

utilizado (*i.e.,* carta remetida por correio). A estratégia testada inclui intervenções automáticas – mensagens de texto curtas (SMS), chamadas e lembretes (etapa 1), chamadas manuais realizadas por secretários clínicos (etapa 2), entrevistas presenciais efetuadas por médicos de família (etapa 3), aplicadas de forma sequencial às mulheres que não aderiram ao rastreio do cancro do colo do útero, após cada uma das etapas.

Os parágrafos seguintes descrevem os objetivos específicos definidos para esta tese, bem como os respetivos métodos e principais resultados:

1) *Testar a superioridade de uma estratégia de convite para o rastreio do cancro do colo do útero, composta pelas intervenções da etapa 1, etapas 1+2 e etapas 1+2+3, em comparação com o método de convite habitual.*

Para responder a este objetivo foi implementado um estudo aleatorizado e controlado, paralelo, multicêntrico e de base populacional (*Stepwise Strategy to improve Cervical Cancer Screening Adherence - SCAN trial),* que incluiu mulheres elegíveis para rastreio do cancro do colo do útero, com idades compreendidas entre os 25 e os 49 anos, inscritas nos Agrupamentos de Centros de Saúde do Porto Ocidental ou Marão e Douro Norte, com um número de telefone móvel disponível. No grupo de intervenção, as utentes foram convidadas através de uma estratégia composta pelas etapas 1 a 3, aplicadas de forma sequencial às mulheres que não aderiram ao rastreio após a implementação da etapa anterior. As mulheres aleatorizadas para o grupo de controlo foram convidadas através de uma carta remetida por correio. Foi considerado como *outcome* primário do estudo a proporção de mulheres rastreadas, após a etapa 1 (avaliado 45 dias após o convite inicial), etapas 1+2 (avaliado 90 dias após o convite inicial) e etapas 1+2+3 (avaliado 150 dias após o convite inicial).

A adesão ao rastreio do cancro do colo do útero foi significativamente superior nas mulheres aleatorizadas para o grupo de intervenção, após a etapa 1 (39,9% vs. 25,7%; p<0,001), etapas 1+2 (48,6% vs. 30,7%; p<0,001) e etapas 1+2+3 (51,2% vs. 34,0%; p<0,001).

De forma a promover a difusão do conhecimento gerado, os resultados da etapa 1 foram comunicados às unidades de cuidados de saúde primários envolvidas no estudo SCAN, através da utilização de relatórios personalizados de acordo com as suas características e interesses.

2) *Comparar a custo-efetividade de uma estratégia de convite para o rastreio do cancro do colo do útero, composta pelas intervenções da etapa 1, etapas 1+2 e etapas 1+2+3, com o método de convite habitual.*

Realizou-se um estudo de avaliação económica, no qual foram utilizados modelos de árvore de decisão, para comparar a custo-efetividade de quatro estratégias de convite para rastreio do cancro do colo do útero: (a) carta remetida por correio; (b) intervenções da etapa 1; (c) intervenções das etapas 1+2; (d) intervenções das etapas 1+2+3. Foi considerado como *outcome* primário do estudo o custo por *quality-adjusted life year* (QALY), assumindo uma janela temporal de análise de cinco anos. A adesão ao rastreio do cancro do colo do útero, após a implementação de cada uma das estratégias de convite, foi obtida a partir do estudo SCAN e convertida em QALYs, de acordo com as orientações descritas na literatura. Os custos incluídos nos modelos económicos foram calculados na perspetiva do prestador e societal, considerando para o efeito custos obtidos do estudo SCAN, bem como fontes de informação nacionais e estudos internacionais. Os benefícios e custos de cada uma das estratégias de convite foram utilizados para calcular rácios de custo-efetividade (*incremental cost-effectiveness ratios*, designados ICER) e comparados com um valor de disponibilidade a pagar de 22398€ por cada QALY (*i.e.*, o valor do produto interno bruto *per capita* de Portugal). A estratégia que apresentou o valor de ICER mais elevado, imediatamente abaixo do patamar de disponibilidade a pagar por QALY, foi considerada como a opção mais custo-efetiva.

Este estudo mostrou que uma estratégia de convite para rastreio do cancro do colo do útero composta pelas etapas 1+2 foi altamente custo-efetiva, com valores de ICER de 4286€ e 9394€, na perspetiva societal e do prestador, respetivamente. Esta intervenção é mais custo-efetiva do que o procedimento de convite habitual, o qual foi fortemente dominado (*i.e.,* estratégia menos efetiva e mais cara do que outra intervenção), mas também superior às intervenções compostas pela etapa 1 ou etapas 1+2+3.

Em conclusão, os resultados desta tese mostraram que uma estratégia de convite com um grau crescente de personalização, baseada em intervenções automáticas (SMS, chamadas e lembretes), chamadas manuais e entrevistas presenciais ou combinações destes componentes, resultou em um aumento da adesão ao rastreio organizado do cancro do colo do útero, em comparação com o procedimento habitual. Adicionalmente, os resultados obtidos suportam a utilização de intervenções automáticas (SMS, chamadas e lembretes) combinadas com chamadas manuais como o método habitual de convite para rastreio do cancro do colo do útero, quando considerada uma disponibilidade a pagar de uma vez o produto interno bruto per capita em Portugal.

1 | INTRODUCTION

Globally, cancer is the second cause of death, just after cardiovascular diseases, and accounts for an expenditure of around 1.5% of the world's gross domestic product.[1,2] In 2018, an estimated 18.1 million new cancer cases and 9.6 million cancer deaths occurred worldwide.[3] Considering both sexes, the most commonly diagnosed cancer was lung cancer (accounting for 11.6% of all cancer cases), followed by breast (11.6%), colorectal (10.2%), prostate (7.1%) and stomach cancer (5.7%).[3,4] Lung cancer was also the first cause of death (accounting for 18.4% of all cancer deaths), followed by colorectal (9.2%), stomach (8.2%), liver (8.2%) and female breast cancer (6.6%).[3,4] Prostate cancer was the second most commonly diagnosed cancer among males, although it was the fifth most common cause of cancer death. Among women, breast was the most frequently diagnosed cancer and the leading cause of cancer death, while cervical cancer ranked fourth, both in number of cases and deaths.[3]

To reduce the impact of cancer, a clear investment on cancer prevention and control interventions is required.[5] For example, the promotion of healthier lifestyles (*i.e.*, regular practice of physical activity, high intake of fruit and vegetables, low consumption of alcoholic beverages, avoidance of smoking) may contribute to reduce the occurrence of the most frequent types of cancer.[6] Hepatitis B and Human Papillomavirus (HPV) vaccines are also cost-effective and easy to implement interventions for the prevention of liver and cervical cancer, respectively.[7,8] Additionally, organized screening is an adequate strategy for reducing cancer morbidity and mortality, through early detection and treatment of breast, colorectal and cervical cancer, or corresponding pre-malignant lesions, as applicable.[9]

1.1 Cervical cancer epidemiology

Cervical cancer is one of the most preventable cancers, both through HPV vaccination and organized screening; however, it was estimated to account for more than half a million new cancer cases in 2018.[3,8,10] As depicted in Figure 1, the age-specific incidence is close to zero for the first age groups and increases with age, peaking at 36.6/100 000 women in the 55-59 age-group and decreasing thereafter.[11]

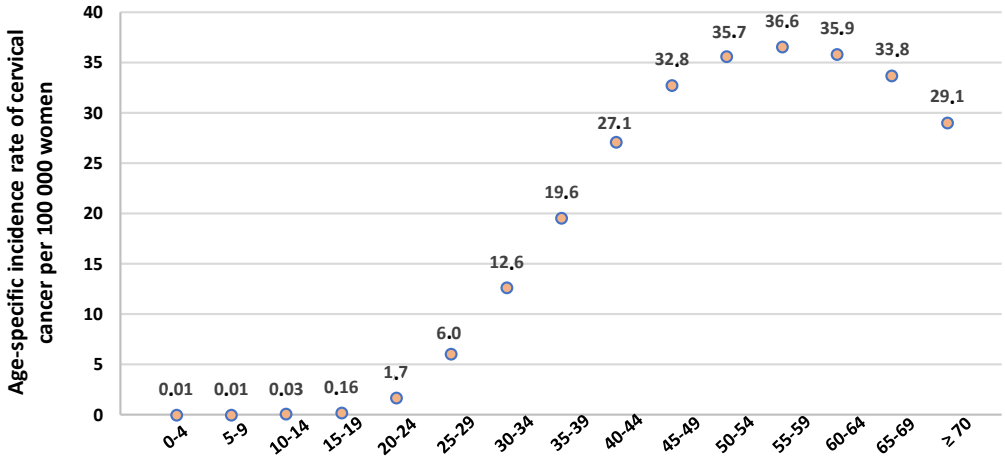

Figure 1. Global age-specific incidence rates of cervical cancer per 100 000 women in 2018. Compiled from Cancer Today (2018).[11]

Cervical cancer is the second most frequent cancer among women in low-income countries, although it ranks twelfth in high-income countries.[4] The age-standardized incidence and mortality rates worldwide are depicted in Figure 2.

After the implementation of organized screening, the age-standardized incidence rates (world standard population) decreased markedly since the 1970s among Northern European countries (*i.e.*, Denmark, Finland, Iceland, Norway, Sweden) and after the 1990s, the rates also decreased in Central and South Europe, North America and some Central and South American countries (*i.e.*, Brazil, Colombia, Costa Rica, Ecuador).[12]

The CONCORD-2 study showed that globally, the age-standardized 5-year net survival rate (International Cancer Survival Standard weights) was above 50% for most countries, although in Europe it ranged from 60 to 69%.[13]

In 2018, cervical cancer was the fourth leading cause of female cancer death in the world, estimated to account for over 310 000 deaths, and ranked third among women aged 15 to 44 years.[4] The age-standardized mortality (world standard population) was 9-fold higher in low-income countries than in high-income countries, with estimates of 22.1 and 2.5/100 000 women, respectively.[4]

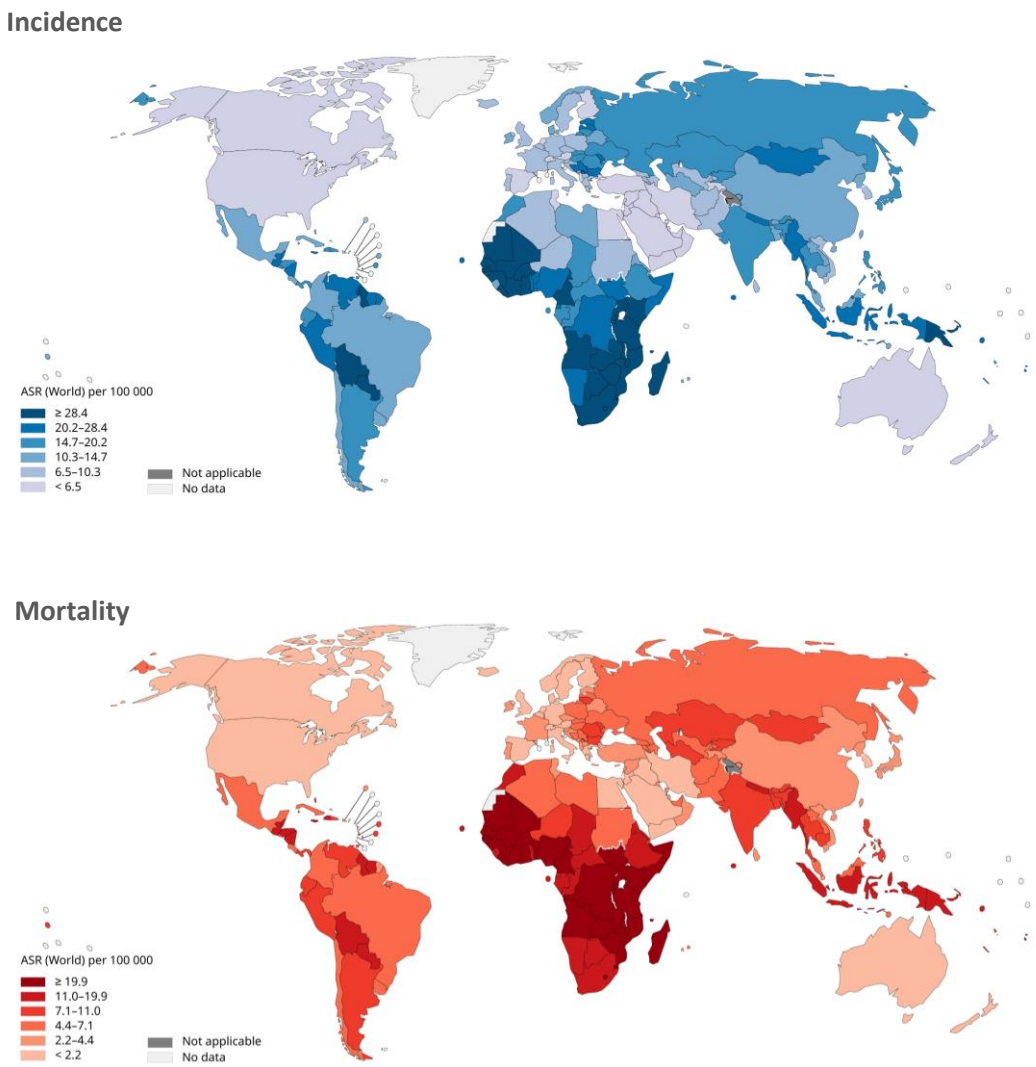

Figure 2. Cervical cancer incidence and mortality rates in 2018.

ASR (World) – Age-standardized rate (world standard population). Reproduced from Cancer Today (2018).[14]

Cervical cancer mortality decreased over the last decades in most countries, which can be explained by the wide implementation of cervical cancer screening and by a reduction in the prevalence of HPV persistent infection.[10,15,16] This reduction in mortality was more notorious among the Nordic European countries, particularly in Iceland and Finland where the age-standardized mortality rates (world standard population) decreased between 1986 and 1995, around 76% and 73%, respectively.[17] The crude incidence rate of cervical cancer is projected to steeply decrease or remain stable until 2030, resulting in half a million to 700 000 new cases of cervical cancer per year.[16]

Cervical cancer is the eighth most common cause of cancer among Portuguese women and accounts for a total of 750 new cases and 340 deaths each year.[18] The age-standardized incidence rate (world standard population) in 2018 was estimated at 8.9/100 000 women, which

is lower than the mean European value of 11.2/100 000 women, although higher than the mean among Western European countries of 6.8/100 000 women.[18] The Portuguese cancer registries only have cervical cancer incidence data for the time-period 2001-2010, however, the available evidence shows a slight decrease in the age-standardized incidence rate (world standard population) from 10.8/100 000 women in 2001 to 8.9/100 000 women in 2010.[19,20]

The Portuguese age-standardized mortality rate of cervical cancer (world standard population) decreased slightly between 1981 and 2018, with corresponding estimates of 3.1 and 2.8/100 000 women.[21] The most recent estimates were lower than the mean European value of 3.8/100 000 women, although higher than the mean value among Western Europe countries of 2.1/100 000 women.[18]

1.2 Pathophysiology and natural history of cervical cancer

Cervical cancer is a neoplasia caused by the persistent infection with HPV, which occurs more frequently in the transformation zone of the cervix, that corresponds to the junction between a stratified squamous epithelium of the ectocervix and a columnar epithelium of the endocervical canal.[10,22] The HPV virus can also cause other malignant tumours, such as cancers of the vulva, anus, penis, vagina or oropharynx, as well as benign lesions, including anogenital condylomas, genital warts or laryngeal papillomatosis.[23–26]

The development of cervical cancer occurs through four main steps: 1) HPV transmission and infection of the cervix epithelium; 2) persistence of the viral infection; 3) progression of the infected cells to a precancerous lesion; 4) invasion of the surrounding tissues.[27] Figure 3 depicts the development of cervical cancer along with the cytohistologic classification of the cervical lesions associated with HPV infection.

The HPV is usually transmitted through sexual contact, that allows the virus to colonize and enter the cervical mucosa using micro abrasions or anatomic small tears of the epithelium.[24,27–29] Most of the infections of the cervix are eliminated or supressed by cell-mediated immunity in one to two years, although some of them may persist and progress to precancerous lesions. The latter are expected to occur if the infection is caused by a high-risk HPV type (*i.e.*, type of HPV that has a high potential to cause cervical cancer), which has the ability to colonize the stem cells of the mucosa and use their machinery to originate newly infected cells that can invade the surrounding tissues.[24,27,28] The low-risk HPV types only unfrequently reach the stem cells and immortalize the viral production, so they have a very limited oncogenic potential.[30]

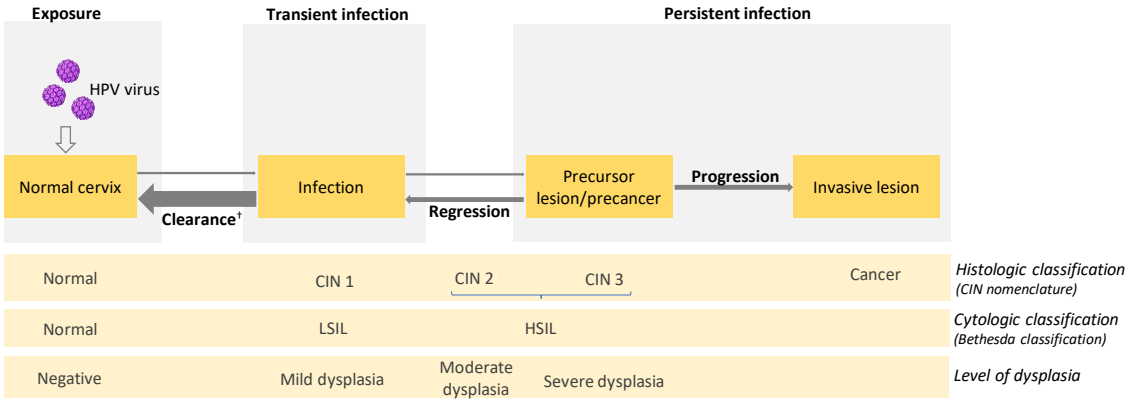

Figure 3. Description of the evolution from HPV infection of the cervix to the development of an invasive cervical cancer and corresponding classification of the lesions. *

CIN - Cervical intraepithelial neoplasia. HPV - Human papillomavirus. HSIL - High-grade squamous intraepithelial lesion. LSIL - Low-grade squamous intraepithelial lesion.

*The thickness of the grey arrows is proportional to the frequency of the described phenomena. †Cell-mediated immunity is responsible for clearing most HPV infections. Source: based on Bosch, F X *et al.* (2002) and Schiffman, M *et al.* (2007).[22,27]

Currently, there is enough evidence to support genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 as high-risk and genotypes 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 as low-risk, although the level of evidence is still limited for genotypes 26, 30, 34, 53, 66, 67, 68, 69, 73, 82, 85, 97.[24,31,32] Genotype 16 is the most frequent, with a global weighted prevalence (calculated as a pooled prevalence of 194 studies, weighted by study size and further standardized by world's geographical structure) among women with no abnormal findings in cytology of 3.2%, followed by genotype 18 with a weighted prevalence estimated at 1.4%.[33] The most commonly detected genotypes in cervical cancer cases are the following, by decreasing frequency: 16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 39, 51, 73, 68 and 66.[34] HPV 16 and 18 were detected in around 70% of all cervical cancer cases worldwide and are also the most commonly identified genotypes in cervical cancer cases in Portugal, with an estimated crude prevalence of 58.2% and 9.2%, respectively.[24,34,35]

Despite carcinogenic potential of HPV infection, other cofactors are also required for the progression from HPV infection to cervical cancer, namely environmental exposures (*e.g.*, contraceptive use, smoking) or host characteristics (*e.g.*, high parity, co-infection with HIV).[24,26] Although uncertainties remain, other cofactors may also promote the progression to cervical cancer, namely the immunosuppression caused by organ transplant, so as the co-infection with *Herpes simplex* virus 2 or *Chlamydia trachomatis*.[24]

HPV epidemiology

The global weighted prevalence of HPV infection (calculated as a pooled prevalence of 194 studies, weighted by study size and further standardized by world's geographical structure), among women with no abnormal findings in cytology, was estimated at 11.7% (95% confidence interval (CI): 11.6% to 11.7%) in 2010.[33] Women aged 0-24 years have the highest weighted HPV prevalence (pooled estimate, weighted by study size and standardized by world's geographical structure), with a value of 24.0% (95% CI: 23.5% to 24.5%), which decreases as women become older, reaching values of 13.9% (95% CI: 13.6% to 14.1%), 9.1% (95% CI: 9.0% to 9.2%) and 4.2% (95% CI: 4.2% to 4.3%), for the age-groups 25-34, 35-44 and 45-54, respectively, although for the age-group ≥55 years the prevalence was higher and estimated at 7.5% (95% CI: 5.0 to 11.0%).[33] This pattern may be explained because young women have sexual relations more often and commonly with more than one partner, increasing the potential to be infected with HPV; while older women more often have a single partner and less sexual relations.[25,30,33] On an analysis by region, the weighted HPV prevalence (pooled estimate, weighted by study size and standardized by world's geographical structure) was lowest in Western Asia (1.7%, 95% CI: 1.1% to 2.5%) and highest in Eastern Africa (33.6%, 95% CI: 30.2% to 37.1%).[33] In Europe, the weighted HPV prevalence (pooled estimate, weighted by study size and standardized by world's geographical structure) was 14.2% (95% CI: 14.1% to 14.4%), with the lowest estimates observed in Southern Europe (8.8%, 95% CI: 8.5% to 9.0%) and the highest in Eastern Europe (21.4%, 95% CI: 20.1 to 22.7%).[33]

1.3 Cervical cancer prevention and control strategies

Reductions in cervical cancer incidence and mortality can be achieved through the implementation of HPV vaccination and organized screening, both being safe, effective and cost-effective interventions recommended by the World Health Organization (WHO).[15,36]

1.3.1 HPV vaccination

The approval for human use of the first HPV vaccine in 2006 challenged the role of organized screening as the main strategy of cervical cancer prevention.[37] This promoted a paradigm shift, from secondary prevention, based on the early detection of malignant and pre-malignant lesions through organized screening, to primary prevention. Currently, a total of three different vaccines targeting HPV were approved for commercial use to prevent cervical cancer: a) bivalent vaccine (Cervarix®, GlaxoSmithKline), targeting HPV types 16 and 18; b) tetravalent vaccine

(Gardasil®, Merck & Co, Inc.), targeting HPV types 6, 11, 16, 18; c) nonavalent vaccine (Gardasil 9®, Merck Sharp & Dohme Corp.), targeting HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58.[38–41] The bivalent vaccine showed an efficacy of 91.6% (95% CI: 64.5% to 98.0%) against persistent infection with HPV 16/18 (*i.e.*, positivity for HPV 16/18 in at least two moments, separated by six months) and 100% (95% CI: 47.0% to 100%) for the prevention of cytological abnormalities produced by HPV 16/18.[38] Additionally, it was also effective against CIN2+ lesions caused by HPV 16/18 in 92.9% (95% CI: 79.9% to 98.3%) of the vaccinated women, after a mean follow-up of approximately three years.[39] The efficacy in the prevention of CIN2+ lesions was higher when the tetravalent vaccine was used, with an estimate of 98% (95% CI: 86% to 100%), after a similar mean follow-up time.[41]

A randomized controlled trial was conducted to compare the immunogenicity and incidence of high-grade cervical, vulvar and vaginal disease in women immunized with the nonavalent vaccine (intervention group) with those submitted to the tetravalent vaccine (control group).[40] The antibody response to HPV 6, 11, 16, and 18 was noninferior in the group of women immunized with the nonavalent vaccine. The crude incidence rate of high-grade cervical, vulvar and vaginal disease caused by any HPV genotype was 14.0/1000-person years in both groups. Additionally, the crude incidence rate of high-grade cervical, vulvar and vaginal disease caused by HPV genotypes 31, 33, 45, 52 and 58 was 0.1/1000 person-years in the intervention group and 1.6/1000 person-years in the control group, with a corresponding efficacy of 96% (95% CI: 80.9% to 99.8%). All vaccines fulfilled high standards of safety and proved to be well tolerated.[38–41]

Many economic evaluations of HPV vaccines were already conducted to support their adoption, at a population level. For example, in the Netherlands it was shown that the use of bivalent HPV vaccines are a cost-effective intervention, with an incremental cost-effectiveness ratio (ICER) of €5815 per quality-adjusted life year (QALY), which is inferior to the national willingness-to-pay threshold of €20 000/QALY.[42] The cost-effectiveness of the combined use of organized cervical cancer screening with an HPV vaccine (bivalent or tetravalent) has been shown in Canada and Germany.[43,44] However, the previously published studies are still insufficient to determine if the nonavalent vaccine is more cost-effective than the bivalent or quadrivalent vaccines, particularly in a scenario of simultaneous implementation of organized screening.[45]

Considering the available evidence, the WHO advocates the inclusion of one HPV vaccine in all National Vaccination Plans, in accordance with the economic resources available in each country.[8] In Portugal, the HPV vaccine was included in the National Vaccination Plan in 2008 and currently the immunization is recommended to all 10-year old girls using two doses of the nonavalent vaccine.[46]

The WHO also defines that even if HPV vaccines are implemented at a population level, organized cervical cancer screening is still needed and will probably remain necessary in the future, even in areas where population access to the HPV vaccine is ensured.[8] This technical position is explained because the population uptake of the HPV vaccine is expected to be largely inferior to 100%, since women may be uninformed or voluntarily not want to be vaccinated.[8,47,48] Additionally, the vast majority of women in the population are no longer in the age-group eligible for HPV vaccination and, therefore, the only preventive strategy available is cervical cancer screening.[8,47,48]

1.3.2 Cervical cancer screening

The development of cervical cancer screening began in 1928 with Papanicolaou, who was the first to describe the use of exfoliative cytology (also referred to as conventional cytology) to identify women with invasive cervical cancer.[49] In this technique, a health professional collects cells from the cervix using a brush and transfers them into a glass slide, which after staining, is submitted to microscopic observation.[49] Three decades later, cytology also started to be used to detect premalignant lesions of the cervix.[15,50] This promoted the wide adoption of cytology as screening method, since it was able to detect both invasive cervical cancer cases as well as precursor lesions.[15,50]

In the beginning of the 1990's, the use of liquid-based cervical cytology allowed an increase in the detection of premalignant lesions, a decrease in the proportion of glass slides with insufficient epithelial cells, as well as a decrease in the time required to perform and interpret a cervical cytology.[15,51] In this screening test, cervical cells are collected and transferred to a liquid preservative solution and, after removing the non-epithelial cells from the sample, a glass slide is prepared for microscopic observation.[15]

The most recently developed screening tests aim the detection of DNA of high-risk HPV strains.[52–54] This type of test is applied to exfoliated cervical cells and has the advantage over cytology of requiring minimal human resources in the lab to process the sample, stain or submit it to microscopic observation.[53] Since the result of the test is achieved with no human intervention, it also reduces the interobserver variability that occurs in cytology while interpreting the glass slides.[53] HPV tests have further improved to simultaneously detect high- and low-risk HPV and are currently available in the market for human use (*e.g.*, Hybrid Capture 2®).[53]

In settings where financial, technical and human resources are scarce, cervical cancer screening may be conducted through the visual inspection of the cervix using acetic acid (VIA), which

requires a low level of technology and organization to be implemented.[55] This method is based on the application of a 3-5% solution of acetic acid in the cervix and a subsequent naked-eye observation of any lesion in the cervix.[55] A malignant or premalignant lesion is identified by its acetowhite color, which is different from the usual reddish color of the cervix.[55] Although VIA has a sensitivity similar to that observed in cytology to detect malignant and premalignant cervical lesions, it has a lower specificity.[15]

The different screening methods available in high-resource settings have been contrasted in several studies. For example, in a randomized controlled trial that included women aged 30-69 years, conventional cytology and high-risk HPV tests were compared as screening strategies to detect cervical cancers and high-grade premalignant lesions.[56] The sensitivity of high-risk HPV tests was higher than conventional cytology in the detection of CIN 2+ lesions, with corresponding estimates of 94.6% (95% CI: 84.2% to 100%) and 55.4% (95% CI: 33.6% to 77.2%). However, the specificity was lower for high-risk HPV tests in comparison with conventional cytology, with values of 94.1% (95% CI: 93.4% to 94.8%) and 96.8% (95% CI: 96.3% to 97.3%), respectively. The different screening methods have also been studied in a pooled analysis of four randomized controlled trials that compared cytology (conventional or liquid-based) with high-risk HPV tests, in women aged 20-64 years followed for a median of 6.5 years.[57] This study showed that the crude incidence rate of cervical cancer was similar between both screening methods during the first two and a half years (incidence rate ratio = 0.79, 95% CI: 0.46 to 1.36). Thereafter, the crude incidence rate of cervical cancer was significantly lower among women submitted to high-risk HPV tests than among those who were tested with cytology (incidence rate ratio = 0.45, 95% CI: 0.25 to 0.81).

Additionally, a recent systematic review of 40 studies estimated that the pooled sensitivity of conventional cytology, liquid-based cytology and high-risk HPV tests in the detection of CIN2+ lesions were 62.5% (95% CI: 46.8% to 76.5%), 72.9% (95% CI: 70.7% to 75.0%) and 89.9% (95% CI: 88.6% to 91.1%), respectively, with a corresponding specificity of 96.6% (95% CI: 94.9% to 98.1%), 90.3% (95% CI: 90.1 to 90.5%) and 89.9% (95% CI: 89.7% to 90.0%).[58]

In summary, high-risk HPV tests have a higher sensitivity detecting CIN 2+ lesions when compared with cytology, despite a slightly lower specificity. Additionally, women who are screened using high-risk HPV tests have a lower incidence rate of cervical cancer cases in comparison with those tested with cytology. Therefore, the available evidence supports the use of high-risk HPV tests as the standard method of cervical cancer screening.

Level of organization – from opportunistic invitations to organized screening

Cervical cancer screening is broadly implemented worldwide, although with heterogeneous levels of organization across regions and countries, ranging from opportunistic invitations to well-organized screening programs with a population-based approach.[59,60] Although both represent relevant strategies of cervical cancer prevention and control, organized screening is more cost-effective and contributes for larger reductions in cause-specific mortality.[15]

The implementation of organized screening requires political will and financial commitment to be stated in a public official document, which should also include the screening test to be used, the interval between screening tests and the age-group to be targeted.[59,61–63] From a technical perspective, it is also relevant to have a clear definition on how to perform the screening test, and how the biological products collected during screening have to be transported and processed in the lab.[59,64,65] Additionally, a clinical guideline should establish the workup strategy and treatment plan to be applied to the participants who test positive in the screening test.[59,64,65]

To achieve high standards of quality, an administrative structure should be created, to monitor screening implementation, assess its' performance and report the obtained results.[59,63] The administrative structure should also ensure that the entire eligible population is systematically identified and invited in each screening round, to maximize the potential of disease prevention and reduce health inequalities.[59,65]

The less organized types of screening, also called "wild" or "opportunistic", are usually provided after the recommendation of a health professional during appointments scheduled for other health purposes or after an individual's decision to undergo screening.[59,60,65]

Cervical cancer screening has long been recognized as an adequate strategy for early detection of cancer and premalignant lesions, with health gains for the population, particularly if it is implemented through well-organized screening programs.[66] The effectiveness of organized screening would be ideally studied using a randomized controlled trial to compare the observed mortality rates among screened and non-screened populations.[15] Although this has never been conducted, the available ecologic studies show a clear decreasing trend in cervical cancer mortality following the implementation of organized screening in many countries, supporting its' positive impact on the population's health.[10] These types of studies were extensively published using data from Nordic countries, where the quality of registries is high and organized cervical cancer screening started to be implemented after the 1960s or 1970s.[17,67] After the full implementation of organized cervical cancer screening, the largest decrease in age-standardized mortality (world standard population) was observed in Iceland, followed by Finland, Sweden, Denmark and Norway, with corresponding reductions of 76%, 73%, 60%, 55% and 43%, between 1986 and 1995.[17] The trends in the incidence of cervical cancer were heterogeneous across

Nordic countries. In Finland and Norway the age-standardized incidence (Norway reference population and world standard population, respectively) increased slightly, immediately after the implementation of organized screening.[68,69] However, an overall decrease of 78% in the age-standardized incidence (Norway reference population) was detected in Østfold (the first region in Norway to implement organized screening) between 1959 and 1977, and a reduction in the age-standardized incidence (world standard population) of around 80% was observed in Finland between 1965 and 1990.[68,69] Iceland reported a significant and continuous decline in the age-standardized incidence (world standard population) of cervical cancer, from 15.7 to 10.4/100 000 women between the periods of 1964-1979 and 1980-1995, respectively.[17] Sweden followed the same pattern, with a decrease in the age-standardized incidence (Swedish census population in 1970) of cervical cancer from 20 to 7/100 000 women between 1968 and 1995, corresponding to a 3.7% reduction/year.[70]

The observed reductions in the overall incidence of cervical cancer in Nordic countries after the implementation of organized screening were mainly due to a decrease in the incidence of squamous cell carcinomas, which corresponds to the histological type of tumour that is prevented when cervical cancer screening is implemented.[10,17,67,68,70] This evidence, along with the clear long-term reductions of the overall incidence and mortality in cervical cancer highly support the effectiveness of organized screening.

Cervical cancer screening in Portugal

In Portugal, organized screening was implemented in 1990, after the approval of the first National Oncological Program.[71] This strategic document defined women aged 25-64 years as eligible for cervical cancer screening, which was implemented by family doctors in primary care units.[71] The *Centro* region was the first to implement a pilot cervical cancer screening program in 1990, followed by *Madeira* in 2004, *Lisboa e Vale do Tejo* in 2007, *Norte and Alentejo* in 2008 and lastly, *Algarve* and *Açores* in 2010.[72] In 2017, the complete coverage of the eligible population in most of the regions was achieved, except for *Lisboa e Vale do Tejo* and *Madeira*, where organized screening was still not fully implemented.[73]

The test considered for cervical cancer screening has changed over time. Conventional cytology was used by family doctors during the pilot tests and initial implementation of organized screening.[71] In 2013, the regions of *Norte* and *Algarve* were already implementing a co-test strategy (*i.e.*, the combined use of liquid-based cytology and high-risk HPV test), as part of organized screening.[72] In the same year, the region of *Alentejo* was using liquid-based cytology and the remaining regions a conventional cytology.[72] In 2017, the high-risk HPV tests were

defined by the Ministry of Health as the screening method to be used nationally for cervical cancer screening, which is currently being adopted by the different regions in the country.[74]

The National Health System provides universal and free of charge access to organized cervical cancer screening.[74] The coordination and quality monitoring of organized screening is performed by the General Directorate of Health (*Direção Geral da Saúde*) and the Regional Health Administrations (*Administrações Regionais de Saúde*).[74] All women aged 25-60 years are considered eligible to be invited, except those who have a previous history of total hysterectomy, diagnosis of cervical cancer or gynaecological signs and symptoms.[74] Eligible women are identified by the primary health care units where they are registered, which invite them to undergo screening every five years.[75] The invitation is performed through a written letter that proposes a date and time for the appointment, and is personalized with the woman's name, the name of the primary care unit and the name of the woman's family doctor. Women may reschedule the appointment, using a phone number that is provided in the written letter or in-person at their primary health care unit.[75] The customization of the written letters is automatically performed by a software (*SiiMA Rastreios*), but each invitation needs to be manually printed, folded and inserted into an envelope by a clinical secretary. Women who attend the appointment are screened by their family doctor, who performs a visual inspection of the uterus and collects cells from the cervix.[75] The biologic products are labelled and transported to a centralized lab where a high-risk HPV test is performed.[74,75] Organized screening coexists with opportunistic invitations that may be performed by family doctors during appointments scheduled for other health purposes or by gynecologists working in the private sector.

Adherence to cervical cancer screening

Despite the global acceptance and implementation of cervical cancer screening, the population adherence is frequently low, even among high-income countries.[59,76] The age-standardized prevalence (world standard population) of cervical cancer screening utilization at least once during women's life (opportunistic uptake or as part of organized screening) was estimated at 67.9% (95% CI: 67.6% to 68.2%), in a survey that comprised 57 countries with different levels of development.[76] However, the age-standardized prevalence (world standard population) of women submitted to cervical cancer screening during the last three years was only 39.6% (95% CI: 39.3% to 40.0%) globally and 18.5% (95% CI: 18.3% to 18.8%) in developing countries.[76]

An analysis of the implementation of organized cervical cancer screening in Europe, conducted in 2017, showed that the population coverage (*i.e.*, proportion of women who are invited for

organized cervical cancer screening among those who are eligible) was 82% among the member states/regions who reported this information.[59] The same document describes an adherence proportion to organized cervical cancer screening among the invited women of only 41%, although this estimate ranged from 10% to 68%, according to the considered state/region.[59]

In Portugal, the uptake of cervical cancer screening by the eligible population was also described. Before the implementation of organized screening, a study conducted in a cohort of adults living in Porto (the second largest city in Portugal), estimated a life prevalence of opportunistic uptake of cervical cancer screening of 91.2%.[77] However, among the previous users of screening, only 6.7% were tested at three to five years intervals (*i.e.*, the recommended periodicity).

In a different study, that considered data of the 2005/2006 National Health Survey and included 2191 women aged 25-64 years, the life prevalence of cervical cancer screening uptake was estimated at 76.5%.[78] This national prevalence comprises the contribution of both opportunistic and organized screening, although the later was only being implemented in the region of *Centro* at the time the study was conducted.[78] The uptake of cervical cancer screening was described to vary widely, being higher in the region of *Norte* (84.9%), followed by *Lisboa e Vale do Tejo* (77.9%), *Algarve* (70.3%), *Centro* (69.4%), *Madeira* (63.1%), *Alentejo* (49.4%) and *Açores* (46.5%).

In 2012, the uptake of cervical cancer screening was also assessed using a representative sample of the Portuguese population.[79] This study included women aged 25-64 years and determined a lifetime prevalence of cervical cancer screening uptake of 71.9% (95% CI: 66.5% to 77.3%), which reflects both the contribution of opportunistic testing and organized screening (covering 40% of the eligible population in Portugal).

In addition to the previously presented data regarding the lifetime use of cervical cancer screening, evidence is also available to characterize the adherence to organized screening. The most recent assessment report of the National Oncologic Plan showed that every year, more than 200 000 women are invited for testing and around 130 000 are screened.[73] The proportion of women who adhered to organized cervical cancer screening, among those who were invited, increased from approximately 30% in 2009 to over 60% in 2016.[73]

Many factors have been described to influence the adherence to cervical cancer screening, which should be considered while designing interventions to promote the participation of the eligible population. For example, higher levels of education[78,80–82], white-collar jobs[83] and a higher income[78,80–83] are associated with a higher adherence to cervical cancer screening. Migrants or women who are non-fluent in the country's mother tongue usually have an inferior adherence to screening.[80,83,84] An association between the infrequent use of primary health care services[78,80,85], being unemployed[82,83] or unmarried[80–83] and a low participation in cervical cancer screening has also been described. Regarding the effect of women's age on adherence to

cervical cancer screening, the published literature provides conflicting results. Some authors showed that the adherence is lower for the age extremes of the target population[77,78,81,83] although others describe that adherence increases with age.[78,80,82,85]

Strategies to improve adherence to cervical cancer screening

Although cervical cancer screening is still recommended, its' financial sustainability will be threatened by the simultaneous implementation of HPV vaccination.[47] This is expected to occur since the number of women that need to be screened to prevent a cancer death will increase, while the fixed costs of organized cervical cancer screening will remain constant (*i.e.*, costs with quality assurance and monitoring, training of the health professionals, development of technical guidelines). Therefore, organized cervical cancer screening needs to be reshaped to ensure its' cost-effectiveness. This may be achieved through larger intervals between screening tests, possibly starting at older ages and using different screening strategies for vaccinated and non-vaccinated women.[47,48,86] In addition to these possible modifications, affordable interventions are also required to increase the population's participation, in order to maximize the efficiency of organized cervical cancer screening.

Many interventions intending to increase adherence to cervical cancer screening have already been evaluated, including: a) reminders – printed letters/postcards[87–93], short message systems (SMS)[94] or operator dependent phone calls[90,91,95–97] used to recall previously non-adherent women or to announce that screening date is due; b) small media[98–102] – printed materials, namely letters, posters or leaflets that are used to describe and promote screening, using different levels of customization; c) one-o-one education[101–103] – interviews conducted by telephone or in person to describe cervical cancer screening, but also to overcome any perceived barrier, that may block adherence to organized screening. A previous systematic review showed that all the mentioned types of strategies were effective, with an absolute median adherence increase of 10.2% (Percentile 25 [P25]-Percentile 75 [P75]: 6.3% - 17.9%) when reminders were used, an increase of 4.5% (P25-P75: 0.2% - 9.0%) following small media and an increase of 8.1% (P25-P75: 5.7% - 17.3%) when one-o-one education strategies were implemented.[104]

Despite the available evidence, only a few studies have tested stepwise interventions, applied sequentially until women adhere to cervical cancer screening.[87,90,91] This type of approach is able to increase adherence at an affordable cost, since more automated and easy to implement interventions could be used first to invite all the eligible population and the remaining non-adherent women would receive highly personalized and more costly strategies. The few studies that used stepwise interventions had no increasing level of customization[105]; did not comprise

low-cost or non-operator dependent strategies[87,90,91]; had no population-based approach, targeting only minority groups or deprived settings[87].

The implementation of strategies to increase adherence to cervical cancer screening at a population level requires evidence of their effectiveness, but also cost-effectiveness, which was reported only occasionally. The CRIVERVA study[97] tested the effect of written letters, written letters + leaflets, written letters + leaflets + reminder manual phone calls in comparison with no intervention and calculated an incremental cost per 1% absolute increase in adherence of €2.8, €11.0 and €13.7, respectively. Other studies reported the incremental cost per additionally performed pap smear. For example, a randomized controlled trial conducted in Sweden tested an intervention based on manual phone calls + written letters in comparison with the standard of care invitation (*i.e.*, written letter) and estimated an incremental cost of €151.4 per additional pap smear[106]. In a different study, interventions based on a written letter + manual phone call, two manual phone calls or two written letters were compared with the standard of care (*i.e.*, written letter) and were estimated to have an incremental cost per additional pap smear of $185 (≈€158), $305 (≈€261) and $1117 (≈€955), respectively.[91]

The few previous studies that reported an economic analysis of strategies to increase adherence to cervical cancer screening have several limitations, namely: a) avoided deaths or quality-adjusted life years (QALYs) were not defined as outcomes in the conducted analyses, considering only adherence to cervical cancer screening as the only benefit[91,95,97,103,106,107]; b) costs were calculated from the provider perspective (*i.e.*, includes the costs incurred by a health institution when providing a health service), but not from the societal perspective (*i.e.*, includes provider costs and the costs incurred by the women to access the service)[91,95,97,103,106,107]; c) discount rates were not applied to future costs or benefits[91,95,97,103,107]; d) the uncertainty of the economic model parameters was not addressed, namely through a sensitivity analysis.[91,95,97,103]; e) training costs of the health professionals required to implement the tested interventions were not considered in the economic model[91,95,97,107].

The ideal invitation to cervical cancer screening should be effective and have an affordable cost per women invited, ensuring a cost-effective balance. An adequate assessment of interventions that may promote adherence to cervical cancer screening is required, namely through the rigorous quantification of their effectiveness and corresponding costs. High-quality cost-effectiveness analyses should be conducted to allow policy makers to compare the different invitation strategies available and decide on their implementation, maximizing the health benefits of the scarce financial resources.

2 | OBJECTIVES

Organized screening and HPV vaccination are effective strategies for reducing cervical cancer mortality. Although the latter is expected to represent the most important strategy to prevent cervical cancer in the future, organized screening will remain necessary at least for non-vaccinated women. However, the sustainability of organized programs may be threatened because adherence to organized screening is often low and the increasing use of HPV vaccination will reduce the number of eligible women. Therefore, affordable interventions able to increase the participation in organized programs are needed to ensure the cost-effectiveness of screening strategies. This may be achieved through the combination of automated and low-cost invitations to cervical cancer screening applied to the entire population and more expensive and patient-tailored interventions for the remaining non-adherent women.

Using a population-based approach, this work intends to assess the effectiveness and cost-effectiveness of an invitation strategy, with an increasing level of customization and cost, to improve women's adherence to organized cervical cancer screening, in comparison with a written letter invitation (*i.e.*, the standard of care). The intervention to be tested includes automated text messages/phone calls/reminders (step 1), manual phone calls performed by clinical secretaries (step 2) and face-to-face interviews conducted by family doctors (step 3), applied sequentially to women remaining non-adherent after each step.

This thesis comprises the following specific objectives:

1) To test the superiority of an invitation strategy based on step 1, steps 1+2 and steps 1+2+3 in relation to the standard of care (Papers I, II, III and IV);
2) To compare the cost-effectiveness of an invitation based on step 1, steps 1+2 and steps 1+2+3 with the standard of care (Paper V).

The first objective was accomplished through a multicentre, parallel, population-based randomized controlled trial (*Stepwise Strategy to improve Cervical Cancer Screening Adherence - SCAN trial*), involving women eligible for cervical cancer screening, aged 25 to 49 years, registered in *Porto Ocidental* or *Marão e Douro Norte* Health Care Areas, with an available mobile phone in the National Health Service database. Women randomized to the control group were invited through a written letter and those randomized to the intervention group were invited through a stepwise strategy based on progressively more complex and costly

interventions targeting women with increasingly high levels of unresponsiveness to screening invitations.

The second objective was addressed through an economic study, that compared the cost-effectiveness of the four competing invitation strategies to cervical cancer screening tested in the SCAN randomized controlled trial. The main outcome of the model was the cost per QALY measured over a five-year time horizon. Adherence to cervical cancer screening after each of the competing interventions was obtained from the SCAN trial and the corresponding QALYs were estimated based on previous studies. Costs were calculated from the societal and provider perspective, and were estimated based on Portuguese sources, or if not available, the international literature.

A detailed description of the methods is provided in the protocol of the randomized controlled trial (Paper I), and in each of the articles/manscripts adressing the specific objectives.

3 | PAPERS

3.1 Paper I

Firmino-Machado J, Mendes R, Moreira A, Lunet N. 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. BMJ Open. 2017;7:e017730.

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 randomised controlled trial

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To cite: Firmino-Machado J, Mendes R, Moreira A, *et al*. 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 randomised controlled trial. *BMJ Open* 2017;**7**:e017730. doi:10.1136/bmjopen-2017-017730

► Prepublication history and additional material for this paper are available online. To view, please visit the journal (http://dx.doi.org/10.1136/bmjopen-2017-017730).

Received 31 May 2017
Revised 14 August 2017
Accepted 21 August 2017

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ABSTRACT

Introduction Screening is highly effective for cervical cancer prevention and control. Population-based screening programmes are widely implemented in high-income countries, although adherence is often low. In Portugal, just over half of the women adhere to cervical cancer screening, contributing for greater mortality rates than in other European countries. The most effective adherence raising strategies are based on patient reminders, small/mass media and face-to-face educational programmes, but sequential interventions targeting the general population have seldom been evaluated. The aim of this study is to assess the effectiveness of a stepwise approach, with increasing complexity and cost, to improve adherence to organised cervical cancer screening: step 1a—customised text message invitation; step 1b—customised automated phone call invitation; step 2—secretary phone call; step 3—family health professional phone call and face-to-face appointment.

Methods A population-based randomised controlled trial will be implemented in Portuguese urban and rural areas. Women eligible for cervical cancer screening will be randomised (1:1) to intervention and control. In the intervention group, women will be invited for screening through text messages, automated phone calls, manual phone calls and health professional appointments, to be applied sequentially to participants remaining non-adherent after each step. Control will be the standard of care (written letter). The primary outcome is the proportion of women adherent to screening after step 1 or sequences of steps from 1 to 3. The secondary outcomes are: proportion of women screened after each step (1a, 2 and 3); proportion of text messages/phone calls delivered; proportion of women previously screened in a private health institution who change to organised screening. The intervention and control groups will be compared based on intention-to-treat and per-protocol analyses.

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

Strengths and limitations of this study

- ► Randomised controlled trial, using a stepwise approach, with increasing complexity and cost of interventions, to improve adherence to organised cervical cancer screening.
- ► Interventions tested are technological and innovative.
- ► Use of a population-based approach and not specific groups or minorities.
- ► Contamination of interventions may occur, because randomisation units are individuals and not primary care units.
- ► Unavailability of women's mobile phone may restrict intervention delivery.
- ► The study is restricted to women aged below 50 years, and therefore the findings may not apply to older women with limited digital literacy skills.

Trial number NCT03122275

INTRODUCTION

Cancer is one of the most important causes of morbidity and mortality, especially in high-income countries.[1] A substantial part of cancer cases can be detected earlier and undergo treatment with curative intent.[2] Improvements in early detection of cancer may be achieved through increases in population awareness, enabling early consultation with health professionals, and screening programmes.[2] Cervical cancer screening is one of the oldest and most effective screening programmes, with relevant decreases in mortality since its implementation.[3] Although the increasing coverage of vaccination against high-risk human papillomavirus strains is expected to play a major role in the prevention of cervical

cancer,[4] screening will still be needed, at least for non-vaccinated women and high-risk groups. With the expected decrease in the number of women eligible for screening, cost reduction, including variable costs (invitation and screening), may be needed to guarantee sustainability.

Currently, in Portugal cervical cancer screening is recommended to be performed every 5 years, for women aged between 25 and 65 years.[5] Women registered at a primary care unit are invited to perform cervical cancer screening through a written letter. At a national level, just over half[3] of the invited women adhere to the cervical cancer screening and 23.5%[6] have never performed screening during life. Limited adherence to screening is expected to contribute to greater cervical cancer mortality rates in Portugal (age-standardised mortality rate: 4.9/100 000),[7] in comparison with the average in Europe's rate (27 countries, age-standardised mortality rate: 3.7/100 000).[7]

Different strategies to increase adherence to cervical cancer screening have been developed and evaluated, including interventions based on patient reminders (written letters,[8–13] operator-dependent phone calls[11 12 14 15] or text messages[16]), small media[17–20] (videos, brochures, pamphlets or fact sheets), mass media[21] and face-to-face educational programmes.[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 US$67/response) than text messages (24% uptake, costing US$100/response) or written letters (19% uptake, costing US$133/response).[16] To our knowledge, no automated (machine performed) and customised 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 customisation or built-in mechanisms for reply to the messages. This method was tested as appointment reminders in hospitals[24] and primary healthcare services,[25] with 10% increases in adherence to scheduled appointments, but also as part of obesity control programmes.[26] Some of these programmes allow for patient interaction, enabling them to make a data input on their health status or simply reply after receiving the intervention.[26] This bidirectional 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/bidirectional phone-delivered interventions on the uptake increase of screening programmes.[27]

Educational programmes 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 programmes are highly tailored to each patient, and therefore difficult to implement at a population level, because these are resource-intensive activities. In a population-based approach, a multistage intervention is needed, implementing first, cheaper and easier-to-use interventions such as text messages and automated phone calls. Women refractory to these strategies should receive more expensive and patient-tailored interventions such as phone calls performed by trained professionals as reminders or face-to-face appointments to provide information on cervical cancer screening. Most of the interventions described in the literature target only deprived populations[8 15 18] or from an ethnic group/social minorities[15 18 19 29] and only a few cases use multistage approaches, where different interventions (written letter invitation, written letter reminder, phone call reminder) were sequentially applied till women adhere to screening.[8]

Objectives

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

Step 1a: customised text message invitation;
Step 1b: customised automated phone call invitation;
Step 2: secretary phone call;
Step 3: health professional phone call and face-to-face appointment.

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

1. To test the non-inferiority of interventions based on step 1a and step 1 (1a+1b), considering a non-inferiority limit of 5%;
2. To test the superiority of the specific components of the multistage intervention corresponding to step 2 and step 3;
3. To quantify the differences in adherence to cervical cancer screening, for the intervention based on step 1 (1a+1b) and multistage interventions based on steps 1 and 2, and steps 1–3, between: a) urban and rural areas; b) younger and older populations; c) deprived and non-deprived populations; d) never versus ever users of organised screening; e) history of regular versus irregular participation in organised screening programmes.
4. To quantify the differences in adherence to cervical cancer screening when using a positive or a neutral content of text messages and automated phone calls, in step 1.

5. To estimate the proportion of women who were undergoing performing cervical cancer screening in private healthcare services who started to be screened in an organised cervical cancer screening programme, after a health professional face-to-face appointment at their primary care unit.

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

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

METHODS AND ANALYSIS

Setting

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

Design

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

Women eligible for cervical cancer screening will be randomised 1:1 within each primary healthcare unit.

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

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

Step 2: manual phone calls performed by secretaries, implemented 1–2 months after step 1, among women remaining non-adherent 1 month after step 1;

Step 3: health professional phone call and appointments, implemented 1–2 months after step 2, among women remaining non-adherent 1 month after step 2.

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

Participants

Inclusion criteria

a. Women aged between 25 and 49 years, and eligible for cervical cancer screening (having started sexual activity, not hysterectomised, not undergoing cervical cancer treatment);
b. Medical registration at any of the primary healthcare units selected for this study.

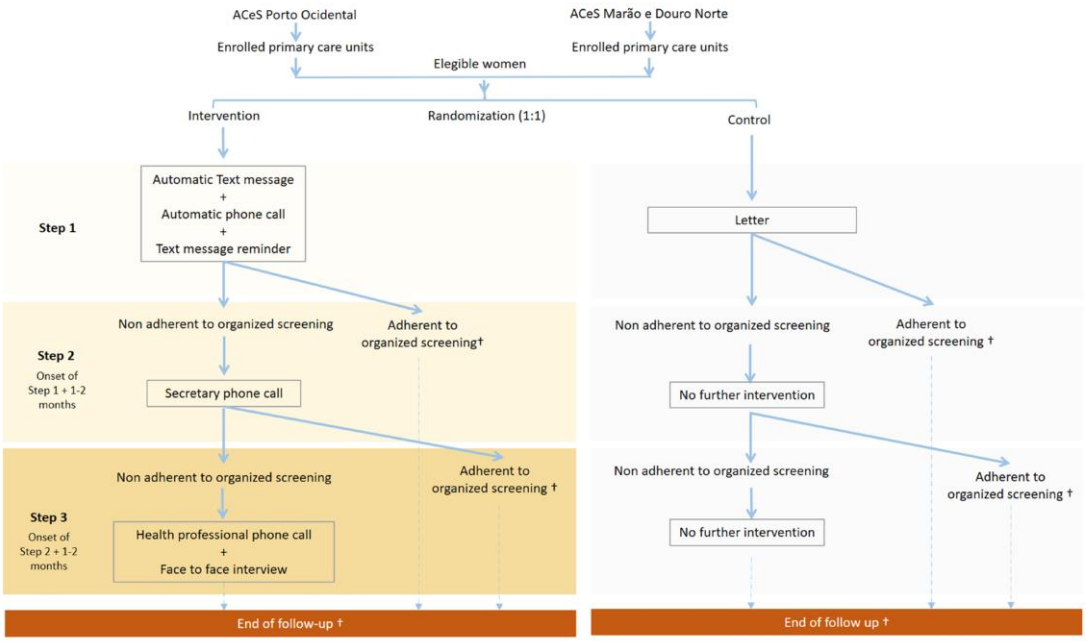

Figure 1 Study design of the stepwise strategy to improve cervical cancer screening adherence. *Outcome assessment.

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

Exclusion criteria

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

Intervention

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

Step 1 (1a+1 b): automated text messages/phone calls

Women randomised to the intervention arm will be assigned a date and hour for screening by the primary healthcare unit secretaries, who will then upload the women's phone number, first and last name, name of the primary care unit and appointment date/hour in the software selected for implementation of step 1: File-2Mail V.2.2, Smart IVR V.1.1, Smart Message V.3.1 and Speech2Go V.1.1. Personalised text messages (step 1a), with a maximum length of 320 characters, and phone calls (step 1b), with a maximum duration of 30 s, will then be automatically assembled and sent to the study participants.

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

Step 1a: automated text messages

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

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

Step 1b: automated phone calls

A phone call invitation will be performed in after-hours period (17–20 hours), using a humanised female voice, and follows the same structure of the text messages (figure 2 and figure 3 invitation phone call 1 and 2). Women will receive phone call 1 if they do not answer the invitation message 1 and receive phone call 2 if they did not answer the invitation message 2.

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

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

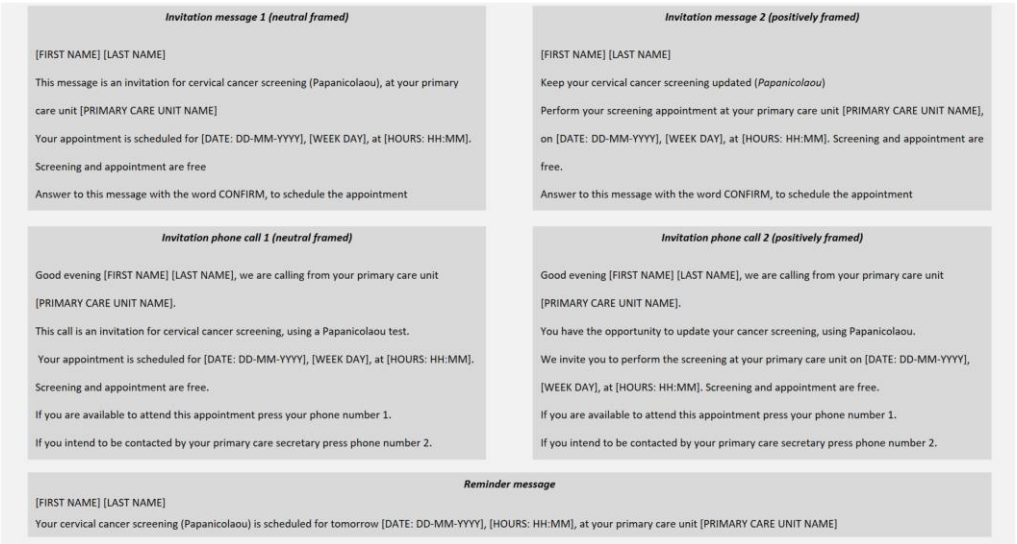

Figure 2 Content for text messages and phone calls.

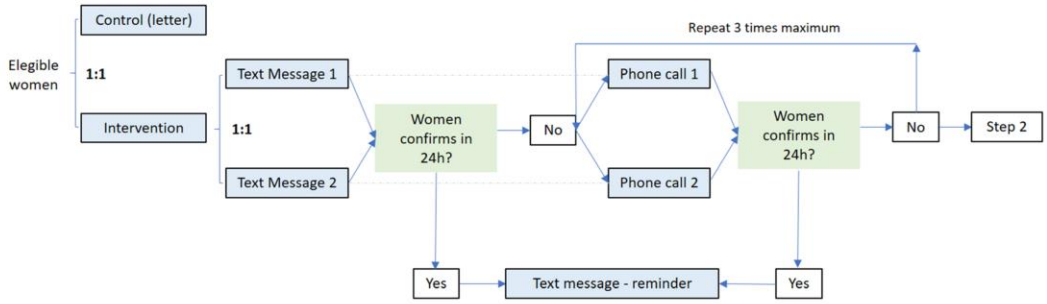

Figure 3 Flow of step 1 interventions: written letter, text messages and automated phone calls.

Step 2: secretary phone call

Women who do not confirm the appointment in step 1 or do not attend organised cervical cancer screening are enrolled in step 2. This comprises an invitation phone call performed in after-hours period (17–20 hours), by the secretary of the corresponding primary care unit. Secretaries will be trained by the research team and will follow a predefined script (see online supplementary appendix 1). If women do not answer the call, it will be repeated daily, for a maximum of 3 days. A date and hour for cervical cancer screening will be scheduled for women who agree to participate.

Step 3: health professional phone call and face-to-face appointment

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

Outcomes

The primary outcome is defined as follows:

Adherence to cervical cancer screening

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

The secondary outcomes are defined as follows:

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

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

Text message status

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

Automated phone call status

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

Change from opportunistic to organised screening

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

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

Sample size

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

Step 1 (1a+1 b)

We estimate an adherence to screening based on invitation through a written letter of 40% (based on SiiMA

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

Steps 1 and 2

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

Steps 1–3

We expect 50% and 70% cumulative adherence proportion in the control and intervention groups, respectively after the interventions based on steps 1–3. In the control group, an increase in comparison to the expected adherence after steps 2, from 45% to 50%, may be anticipated due to the longer period between baseline and outcome assessment. The magnitude of increase in adherence in the intervention group was estimated based on the previously observed effectiveness of face-to-face appointments in other settings.[20] The minimum sample size determined for each group is 134 women.

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

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

Randomisation

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

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

Data collection

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

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

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

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

Statistical analysis

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

1. women who receive the invitation
   - experimental arm: women who receive a text message/phone call, as confirmed by the software used for automated delivery of the intervention
   - control arm: women who received a written letter, that is, no invitation letter returned
2. women who have an appointment scheduled:
   - experimental arm: women who confirm the appointment by replying to the text message or automatic phone call invitation
   - control arm: women assumed to have received the invitation letter with the appointment scheduled, that is, letter not returned.

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

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

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

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

Ethics and dissemination

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

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

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

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

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

Contributors All the authors of the manuscript follow the four criteria of authorship defined by ICMJE. A description of responsabilities/author can be found below: JãF-M. Protocol responsibilities: conceptual design of the research project, drafted the first version of the protocol manuscript and final manuscript production. Study implementation responsibilities: responsible for study presentation and enrolment of all primary care units, intervention implementation, data collection and analysis and manuscript writing. RM. Protocol responsibilities: conceptual design of the research project and critical review of the manuscript. Study implementation responsibilities: responsible for study presentation and enrolment of the primary care units from ACeS Marão e Douro Norte, intervention implementation and data collection. AéM. Protocol responsibilities: conceptual design of the research project and critical review of all protocol drafts. Study implementation responsibilities: responsible for study presentation and enrolment of the primary care units from ACeS Porto Oriental, intervention implementation. NL. Protocol responsibilities: conceptual design of the research project and critical review of all versions of the manuscript. Study implementation responsibilities: responsible for the supervision of the study implementation, data collection and analysis and writing of the manuscripts. All the authors gave a final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding This work is supported by the groups of primary healthcare units involved in the study (ACeS Porto Ocidental and Marão e Douro Norte) and the Instituto de Saúde Pública da Universidade do Porto (ISPUP). The groups of primary care units contribute with the human resources involved in the field work and data collection. The cost of text messages and phone calls are supported by ACeS Porto Ocidental and ISPUP.

Competing interests None declared.

Ethics approval Comissão de Ética da Administração Regional de Saúde do Norte (number 20/2017) and Portuguese National Data Protection Committee (number 11467/2016).

Provenance and peer review Not commissioned; externally peer reviewed.

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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 randomised controlled trial

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BMJ Open 2017 7:
doi: 10.1136/bmjopen-2017-017730

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.

Appendix 2 – Health professional face-to-face interview

Health professional face-to-face interview

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

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

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

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

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

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

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

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

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

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

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

END

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

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

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

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3.2 Paper II

Firmino-Machado J, Vilela S, Mendes R, Moreira A, Lunet N. Stepwise strategy to improve cervical cancer screening adherence (SCAN-Cervical Cancer) – Automated text messages, phone calls and reminders: population based randomized controlled trial. Prev Med. 2018;114:123–33.

Preventive Medicine 114 (2018) 123–133

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Stepwise strategy to improve cervical cancer screening adherence (SCAN-Cervical Cancer) – Automated text messages, phone calls and reminders: Population based randomized controlled trial

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ARTICLE INFO

Keywords:
Mass screening
Early detection of cancer
Uterine cervical neoplasms
Text messaging
Reminder systems

ABSTRACT

The aim of this study was to test the effectiveness of invitation to cervical cancer screening through a very low-cost strategy based on automated and customized text messages, phone calls and reminders. A randomized (1:1) controlled trial was conducted among 13 Portuguese primary care units, recruiting women aged 25 to 49 years, eligible for cervical cancer screening, with an available mobile phone number. In the intervention group, participants were invited for cervical cancer screening through automated/customized text messages and phone calls, followed by text message reminders. Participants in the control group were invited through a written letter (standard of care). The primary outcome was the proportion of women adherent to screening up to 45 days after invitation and the secondary outcome was defined as the adherence proportion after invitation based only on text messages and reminders. A total of 1220 women were randomized, 605 to intervention and 615 to control group. The adherence to cervical cancer was significantly higher among women assigned to intervention (39.0% vs. 25.7%, $p < 0.001$); this corresponds to a difference of 13.3% (95% CI 8.1 to 18.5). The difference in adherence between an invitation strategy based only on text messages and reminders and the standard of care was −0.4%, 95% CI −5.3 to 4.5. In conclusion, an invitation to cervical cancer screening using automated text messages/phone calls and reminders increases the adherence to cervical cancer screening. Such a low-cost and operator-independent strategy of invitation may contribute to the sustainability of organized screening programs.

Trial registration number:NCT03122275.

1. Introduction

Cervical cancer (CC) incidence and mortality are highly sensitive to prevention and control efforts (WHO, 2007), namely through well-organized screening programs (IARC, 2005) and vaccination against high-risk Human Papillomavirus (HPV) (Harper et al., 2004). Although the latter may represent the most important strategy for prevention of CC in a near future, screening of non-vaccinated women and high-risk

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https://doi.org/10.1016/j.ypmed.2018.06.004
Received 12 February 2018; Received in revised form 24 April 2018; Accepted 8 June 2018
Available online 09 June 2018

groups remains necessary. However, the sustainability of organized programs requires increasingly efficient strategies for screening, since the adherence is often low and HPV vaccination will reduce the number of women at a high risk of having CC (European Comission, 2017)

The level of organization (opportunistic screening vs. organized programs) and implementation methodology (e.g. invitation, tests, quality control) of CC screening vary substantially between regions (European Comission, 2017; Gakidou et al., 2008). These differences, along with the cultural and socio-economic diversity of the target groups, translate into heterogeneous results across settings (Martín-López et al., 2012; Miles-Richardson et al., 2017; Limmer et al., 2014; Selvin and Brett, 2003; Richard et al., 2015), showing an ample margin to share the most well succeeded models and test innovative strategies to promote a wider participation with the lowest possible cost.

Many interventions aiming to improve adherence to CC screening have been tested, including face-to-face motivational interviews (Valanis et al., 2002; McAvoy and Raza, 1991), small media (videos or printed materials) (McAvoy and Raza, 1991; Byles et al., 1995; Rimer et al., 1999; Taylor, 2002) or reminder systems (written letters (Lantz et al., 1995; Buehler and Parsons, 1997; Morrell et al., 2005; Eaker et al., 2004; Vogt et al., 2003; Jensen et al., 2009), operator dependent phone calls (Eaker et al., 2004; Vogt et al., 2003; Broberg et al., 2013; Dietrich et al., 2006) or text messages (Marhayu et al., 2014)). These, although effective (around 10% adherence increase (Baron et al., 2008)), are usually demanding in terms of human resources and costs, which often compromises their implementation at a population level (Rimer et al., 1999; Taylor, 2002; Lantz et al., 1995; Morrell et al., 2005; Dietrich et al., 2006). Additionally, most studies targeted selected deprived populations (Rimer et al., 1999; Lantz et al., 1995; Dietrich et al., 2006) or ethnic groups/social minorities (Rimer et al., 1999; Taylor, 2002; Dietrich et al., 2006; Paskett et al., 1999).

Therefore, we aimed to assess the effectiveness of a population-based intervention to invite women for CC screening, based on an automated and low-cost strategy. We tested the superiority of invitation through automated and customized text messages, phone calls and reminders, in relation to the standard of care. The secondary objectives were: a) to test the non-inferiority of an invitation based exclusively on automated text messages in comparison with the standard of care; b) to quantify the differences in adherence to CC screening when using a positive (nudge content) or a neutral framing of text messages and automated phone calls; c) to quantify the differences in adherence to CC screening, for the intervention based on text messages and automated phone calls, between: urban and rural areas; deprivation of the place of residence (least, intermediately and most deprived); younger and older populations; frequency of attendance at organized screening programs (never, irregular or regular attendance).

2. Methods and analysis

A stepwise approach to improve the adherence to organized CC screening was evaluated in a multicentre, parallel, population-based randomized controlled trial – *Stepwise strategy to improve Cervical Cancer Screening Adherence* (*SCAN-Cervical Cancer*). It comprised the use of text messages, automated phone calls and reminders, as well as manual phone calls and health professional appointments, applied sequentially to participants remaining non-adherent after each step, as previously described in detail (Firmino-Machado et al., 2017). Here we report on the comparison of the first set of interventions tested in SCAN-Cervical Cancer, namely automated and customized invitation text messages, phone calls and reminders, with the standard of care (invitation by written letter).

2.1. Setting and participants

In Portugal, CC screening is recommended for women aged 25–65 years, every five years, as part of an organized program, except for those with history of total hysterectomy, diagnosis of CC or gynaecologic signs and symptoms (Ministry of Health, 2017). Eligible women are invited by the primary care unit where they are registered through a written letter, though women may also be opportunistically invited by their family doctors for testing, during appointments scheduled for other reasons, even in areas where an organized program is being conducted.

The present study was conducted among women aged 25–49 years, eligible for screening and registered at primary health care units that perform systematic written letter invitations for screening. Women with no mobile phone number available at the National Health Service database were excluded.

Two Health Care Areas in the north of mainland Portugal were selected: *Porto Ocidental* (PO) and *Marão e Douro Norte* (MDN). The first is a densely populated urban area, where approximately one-third of the women adhere to CC screening (Anon., n.d.-a), and the second serves a predominantly rural area, with an adherence just over 60% (Anon., n.d.-a). In PO there were 15 primary care units, from which four were excluded because screening was not based on systematic invitation and nine participated. In MDN, from the 14 primary care units, all eligible, four participated. All medical doctors from the participant units were invited and 36 (53.7%) participated (Fig. 1).

2.2. Randomization and blinding

In each primary care unit, the list of potential participants was extracted by the clinical secretaries, from the software available to manage the organized cancer screening programs in Portugal. The principal investigator generated the 1:1 randomization sequence, stratified by geographical area (PO and MDN) and Primary Health Care Unit, which was used by the clinical secretaries to assign participants to intervention or control groups. Participants, research team and health professionals were not blinded.

2.3. Intervention

The intervention consisted in invitation to CC screening through automated/customized text messages and phone calls, followed by text message reminders of the appointments (Fig. 2). A text message customized with women's first and last name, name of the primary care unit and appointment date/h was sent as invitation method, approximately 45 days prior to the proposed appointment date. If the text message was not delivered successfully, a new attempt was performed on the following day. This invitation, asked women to confirm the appointment by texting back the word “CONFIRM” (equivalent responses were also considered). Whenever women did not reply, or the text message was not sent after two attempts, an automated and customized phone call was performed to invite women once again. This phone call was performed through an IVR system (Interactive Voice and Response) and followed the same structure of the text message. During the phone call, women were asked to press phone number 1 for appointment confirmation or phone number 2 to reschedule. When

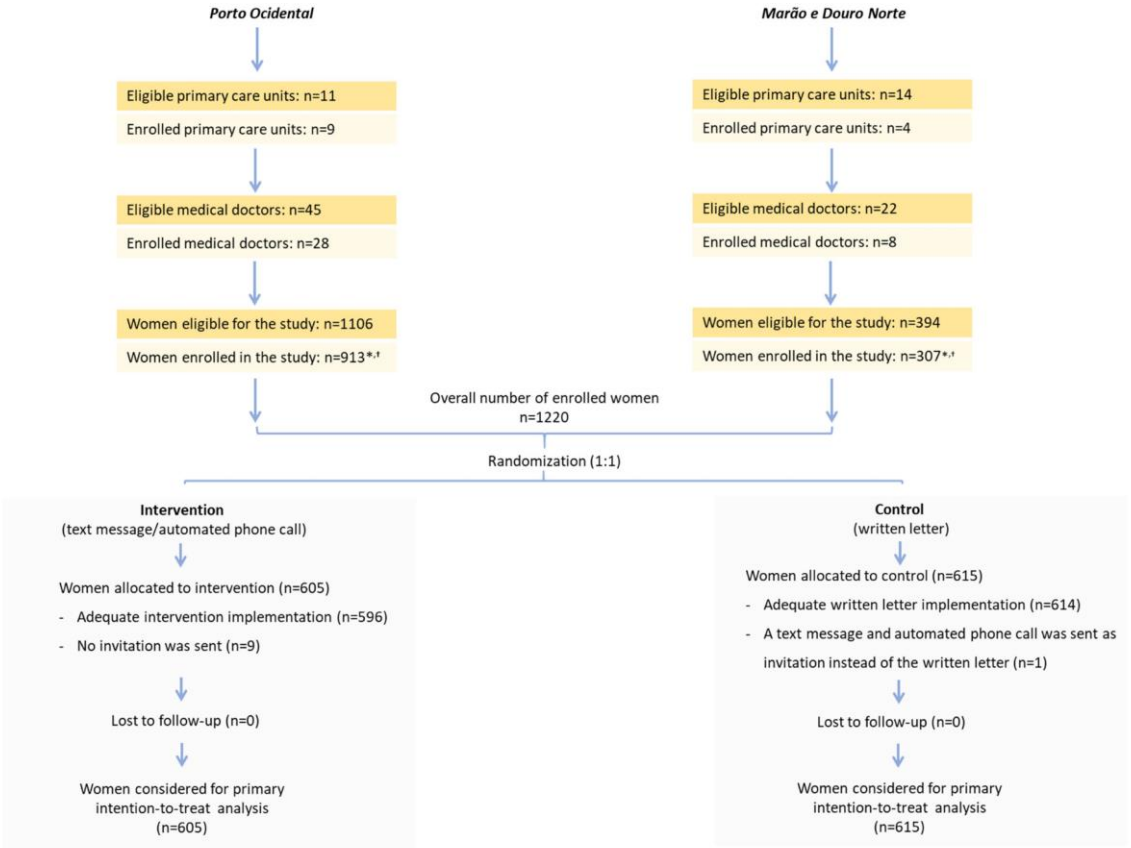

Fig. 1. Enrolment, allocation, follow-up of participants and consequent analysis.
*A total of 27 women (11 from *Porto Ocidental* and 16 from *Marão e Douro Norte*) were excluded since they had no mobile phone number available at the national health services database. †A total of 33 physicians agreed to enrol all eligible women from their lists of patients; due to restrictions of the medical doctors' workload, three medical doctors enrolled only a random sample of their eligible patients.

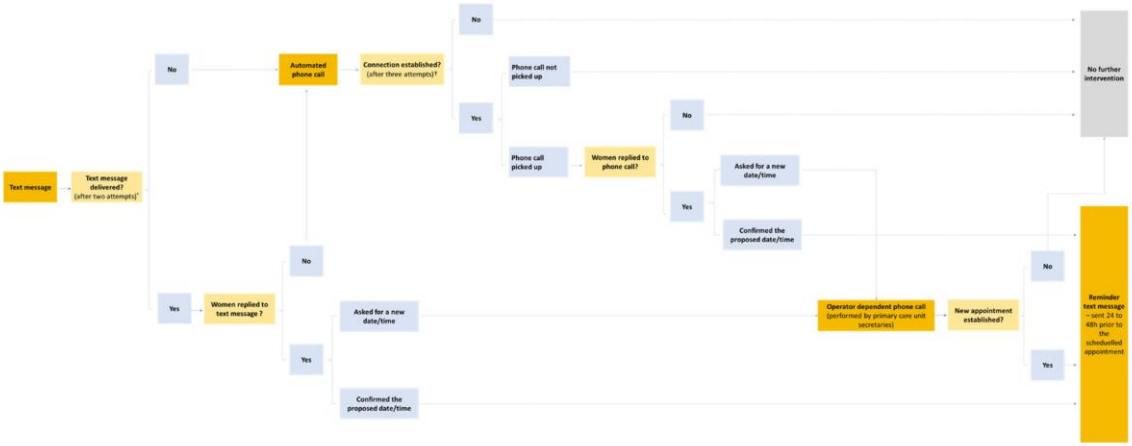

Fig. 2. Implementation of the intervention: text messages, automated phone calls and reminders.
*When the text message was not delivered successfully a new attempt was performed on the following day. †When the connection was not established, or women did not reply, a new phone call was performed on the following day, for a maximum of three days.

women did not press any of the required numbers, the IVR system performed a new phone call on the following day, for a maximum of three days.

When women replied to the invitation text message or phone call asking for rescheduling, they were contacted by the primary care unit secretary on the following day. When a screening appointment was accepted, a reminder message was sent 24–48 h before the appointment.

Participants in the intervention group were randomly assigned to one of the two models of invitation, to be used both in text messages and automated phone calls: neutral – invitation performed using a formal writing to inform women that a screening appointment was scheduled (standard communication style in primary care); positive – women invited using a motivational communication style, intending to nudge them to adhere to CC screening, while letting them know an appointment was scheduled.

The implementation of this intervention requires prior training of health professionals and supervision when starting to use the software. After this initial phase, the tested strategy is expected to cost up to 0.10€/women invited, if it starts to be regularly used at a national level. This estimate comprises the costs with software, salaries of the health professionals that use the software and the subscription of a phone call service.

2.4. Control

The control group received the standard of care, which corresponds to an invitation to CC screening through a written letter. This invitation is sent approximately 45 days prior to the proposed appointment date and has the same level of customization of text messages/automated phone calls. The written letter included instructions for rescheduling the appointment.

As currently implemented, the cost per invitation is approximately 0.80€, comprising the human resources needed for printing and enveloping the invitation and the post-office service.

2.5. Outcomes

Primary and secondary objectives will be addressed based on the following outcomes and indicators (Appendix A): a) proportion of women who were screened on the scheduled date, among those who were invited through text messages and automated phone calls, or text messages only; b) proportion of text messages successfully sent; proportion of picked up automated phone calls; proportion of successfully delivered written letters.

Delivery status of text messages and automated phone calls was collected from the software used to implement these interventions. Outcome assessment was performed on the day after the scheduled appointment (initially proposed or after rescheduling).

2.6. Sample size

We estimated that 1038 woman would be needed to address the primary objective, assuming an adherence of 40% with the standard of care and 50% with the intervention, considering a significance level of 5% (two-sided), a statistical power of 90% and a 1:1 randomization ratio. A 10% adherence increase could be expected because the intervention is based on two consecutive invitation techniques and a reminder text message (Baron et al., 2008).

2.7. Statistical analysis

The primary strategy of data analysis for all the comparisons of adherence between intervention and control groups was intention-to-treat (ITT). Per-protocol analyses were also conducted, considering only women who fulfilled the following criteria:

a) women to whom a CC screening invitation was delivered (intervention – message or phone call successfully delivered; control – written letter not returned);
b) women who confirmed the appointment (intervention – reply to the text message or automatic phone call; control – written letter not returned and appointment not unscheduled).

This study was primarily designed to test the superiority of an invitation based on text messages, automated phone calls and reminders, in relation to the standard of care. Although invitation through text messages followed by automated phone calls corresponds to an intervention with a gradation of intensity, testing the non-inferiority of an invitation based exclusively on the automated text messages, which may be more easily implemented and at a lower cost, was also preplanned, assuming a 5% non-inferiority margin.

Chi-squared tests were used to test differences in the proportion of adherent women between intervention and control groups. Binary logistic regression was used to adjust for differences in the participants' characteristics between intervention and control groups in all per-protocol analyses, but also to control for residual confounding in ITT analysis; OR estimates were adjusted for a previously defined set of potential confounders, which are described in detail in Table 2 and Appendix B.

Additionally, intervention and control were compared in stratified analyses, according to age ($< 35 / \geq 35$ years), Health Care Area (*PO/MDN*), previous participation and frequency of attendance at organized screening (never, irregular or regular attendance).

All p-values are two-sided, except for the non-inferiority analysis that considered one-sided p-values.

3. Results

3.1. Participants

As depicted in Fig. 1, a total of 1220 woman were enrolled between April and October 2017; 605 were randomized to intervention and 615 to control. Among the former, no invitation was sent to nine participants. Among the latter, one participant received a text message and an automated phone call instead of the written letter. Women were followed up to December 2017; there were no losses to follow-up and, therefore, all participants were considered for the ITT analysis.

As depicted in Table 1, at baseline the intervention and control groups were similar in terms of sociodemographic characteristics and previous adherence to CC screening.

3.2. Delivery of invitations for screening

Fig. 3 depicts a detailed description of screening invitation and adherence. Text messages were sent to the 605 participants in the intervention group and successfully delivered to 488 women (80.7%). A total of 378 women, including those who did not reply to the text messages or to whom the text message invitation was not delivered, were also invited through automated phone calls. From the 615 written letter invitations, 6 (1%) were returned by the post office.

Table 1
Baseline characteristics of the participants.

		Participants		
		All (n = 1220)	Intervention (n = 605)	Control (n = 615)
		n (%)	n (%)	n (%)
Age (years)	25–34	626 (51.3)	307 (50.7)	319 (51.9)
	35–49	594 (48.7)	298 (49.3)	296 (48.1)
Education (years)[a]	< 9	62 (10.3)	30 (10.1)	32 (10.6)
	9–11	90 (15.0)	40 (13.4)	50 (16.5)
	12	130 (21.6)	59 (19.8)	71 (23.4)
	> 12	319 (53.1)	169 (56.7)	150 (49.5)
Household size (number of people including the participant)	1 or 2	623 (51.1)	301 (49.8)	322 (52.4)
	> 2	597 (48.9)	304 (50.2)	293 (47.6)
Employment status[b]	Student	52 (4.6)	23 (4.1)	29 (5.1)
	Employed	817 (71.9)	423 (75.0)	393 (68.7)
	Unemployed	251 (22.1)	110 (19.5)	141 (24.7)
	Retired	17 (1.5)	8 (1.4)	9 (1.6)
Occupation (among employed)[c,d]	Blue collar	107 (25.2)	52 (22.8)	55 (27.9)
	White collar	318 (74.8)	176 (77.2)	142 (72.1)
Health Care Area	*Porto Ocidental*	913 (74.8)	445 (73.6)	468 (76.1)
	Marão e Douro Norte	307 (25.2)	160 (26.4)	147 (23.9)
Deprivation index of the place of residence [e,f]	≤ −1.774 (least deprived)	461 (38.0)	221 (36.8)	240 (39.1)
	−1.773 to −0.605	151 (12.4)	70 (11.6)	81 (13.2)
	−0.606 to 0.338	168 (13.8)	86 (14.3)	82 (13.3)
	0.339 to 1.581	169 (13.9)	83 (13.8)	86 (14.0)
	≥1.582 (most deprived)	266 (21.9)	141 (23.5)	125 (20.4)
Previous participation in organized screening and frequency of attendance[g]	Never attended	443 (36.3)	210 (34.7)	233 (37.9)
	Attended irregularly	536 (43.9)	276 (45.6)	260 (42.3)
	Attended regularly	241 (19.8)	119 (19.7)	112 (19.8)

[a] Data missing for 619 participants.
[b] Data missing for 83 participants.
[c] Data missing for 392 participants.
[d] According to the International Standard Classification of Occupation.
[e] Could not be computed for five participants living outside Portugal.
[f] Based on the Portuguese version of the European Deprivation Index: – the quintiles of the distribution in Portugal, were used as cut-offs (Ribeiro et al., 2017).
[g] Adherence to the three previous screening rounds of organized cervical cancer screening was classified as regular attendance.

3.3. Intention-to-treat analysis

As depicted in Table 2, the adherence to CC screening was significantly higher among women assigned to intervention (39.0%) than in the control group (25.7%); this corresponds to a difference of 13.3% (95% CI 8.1 to 18.5), and a "number needed to invite" of 7.5. The odds ratio was 1.85 (95% CI 1.45 to 2.36).

The effect of an invitation based only on text messages and reminders was non-inferior to control, with an adherence of 25.3% in the intervention and 25.7% in the control group, corresponding to a difference of −0.4%, 95% CI −5.3 to 4.5 (p = 0.967).

According to the stratified analyses (Table 2), the effectiveness of the intervention was higher among women aged 35–49 years (OR = 2.31, 95% CI 1.63 to 3.27), from the Porto Health Care Area (OR = 1.97, 95% CI 1.49 to 2.60), living in a more deprived area (OR = 1.98, 95% CI 1.28 to 3.05) and among those who did not participate regularly in organized screening (OR = 2.12, 95% CI 1.47 to 3.05).

The adherence to CC screening was not significantly different between neutral and positive text messages/phone call invitations (36.7% vs. 40.8%, p = 0.298).

3.4. Per-protocol analyses

Considering only the women to whom a CC screening invitation was delivered, the adjusted OR was 2.14 (95% CI 1.66 to 2.77). The estimated effect of the intervention was strongest when the analysis was restricted to women who confirmed the appointment ($OR_{adjusted}$ = 4.19, 95% CI 3.12 to 5.64). Stratified per-protocol analyses are presented in Appendix B.

The adjusted ORs for the effect of invitation based only on text messages and reminders were 1.27 (95% CI 0.97 to 1.65) among women to whom a CC screening invitation was delivered and 5.74 (95% CI 4.10 to 8.03) in those who confirmed the appointment.

4. Discussion

An automated and easy-to-implement strategy based on customized text messages, phone calls and reminders for invitation to CC screening was significantly more effective than the standard of care.

The per-protocol analysis considering only the women who confirmed the appointment yielded an adherence of 60.1% in the intervention group, corresponding to the maximum effect possible to achieve with this strategy. This is higher than the observed in the ITT analysis (39.0%), reflecting the fact that only 80% of the participants received the invitation text message and < 60% of the phone call attempts were established. Therefore, the gap between efficacy and effectiveness of the intervention may be expected to decrease substantially with more up to date phone number records (Ministry of Health, 2015).

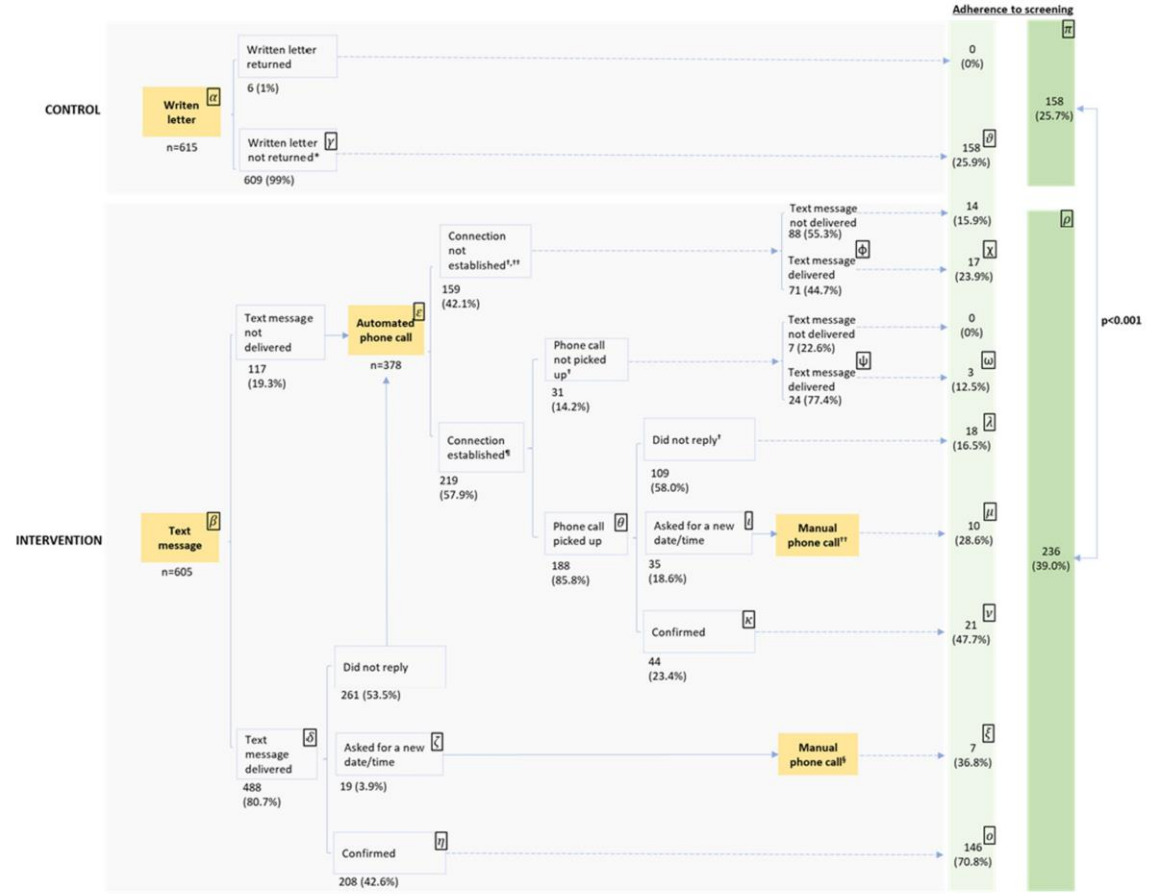

Fig. 3. Delivery of invitations and adherence to screening among intervention and control groups.
Figures represent the absolute number (proportion of women) in each group. Greek letters identify the number of participants to be considered to compute the outcomes (Table 1 for details).
*There were not appointments unscheduled. †Women not confirming screening appointments may undergo opportunistic screening. ††Includes 88 women to whom a text message was not delivered and 71 of those who did not reply to the text message. ¶Includes 29 women to whom a text message was not delivered and 190 of those who did not reply to the text message. §All the women who asked for a new appointment date/time picked up the phone call performed by the primary care unit secretaries.

Multistage strategies based on the use of written letters and manual phone calls were previously shown to be effective; however, they were highly operator dependant, limiting the generalization of its use (Eaker et al., 2004). The present trial shows that this limitation may be overcome with fully automated invitation procedures.

The effectiveness of the tested intervention was greater among older women and previous attenders of CC screening. A more frequent use of primary health care services by these participants, and therefore more updated phone number registers, may contribute to the differences observed, which is supported by our data. Since mobile technologies are highly used > 98% of the Portuguese population use a mobile phone daily (Anon., n.d.-b) and there is an ongoing update of phone number registers, these differences in the effectiveness of the intervention may be expected to decrease in a near future.

The effectiveness of the tested strategy was similar for women with different levels of deprivation, supporting its use among the most deprived, who have been previously shown to have a lower adherence to CC screening (Limmer et al., 2014).

The literature is conflicting regarding the way invitations should be framed to increase the adherence to CC screening (Rothman et al., 2006). In our study, there were no significant differences in adherence between neutral and positive styles of invitation. The small number of characters used for text messages/phone calls may have contributed for women to have the same perception of both communication strategies.

The cost per invitation was previously described to range between 4.5€, for an invitation performed through a text message (Marhayu et al., 2014) to over 30€, when written letters and manual phone calls are used (Vogt et al., 2003). Although the description of these

Table 2
Intention-to-treat analysis for the comparison between intervention and control groups.

	Intervention			Control			% Difference (95% CI)	p value[a]	Crude OR (95% CI)	Adjusted[b] OR (95% CI)
	n	$n_{adherent}$	% adherence	n	$n_{adherent}$	% adherence				
Intention-to-treat analysis of adherence										
All women	605	236	(39.0)	615	158	(25.7)	13.3 (8.1 to 18.5)	< 0.001	1.85 (1.45 to 2.36)	1.87 (1.46 to 2.39)
Age (years)										
25–34	307	105	(34.2)	319	83	(26.0)	8.2 (1.0 to 15.3)	0.026	1.48 (1.05 to 2.08)	1.49 (1.05 to 2.11)
35–49	298	131	(44.0)	296	75	(25.3)	18.6 (11.0 to 25.9)	< 0.001	2.31 (1.63 to 3.27)	2.34 (1.64 to 3.34)
Health Care Area										
Porto Ocidental	445	181	(40.7)	468	121	(25.9)	14.8 (8.7 to 20.8)	< 0.001	1.97 (1.49 to 2.60)	1.95 (1.47 to 2.60)
Marão e Douro Norte	160	55	(34.4)	147	37	(25.2)	9.2 (−1.1 to 19.1)	0.079	1.56 (0.95 to 2.56)	1.60 (0.96 to 2.65)
Deprivation of the place of residence[c]										
Least deprived	262	99	(37.8)	295	70	(23.7)	14.1 (6.4 to 21.6)	< 0.001	1.95 (1.35 to 2.82)	1.91 (1.31 to 2.77)
Intermediately deprived	153	54	(35.3)	143	37	(25.9)	9.4 (−1.1 to 19.6)	0.079	1.56 (0.95 to 2.58)	1.58 (0.95 to 2.61)
Most deprived	186	83	(44.6)	176	51	(29.0)	15.7 (5.7 to 25.1)	0.002	1.98 (1.28 to 3.05)	2.05 (1.30 to 3.21)
Previous participation in organized screening and frequency of attendance										
Never attended	210	48	(22.9)	233	41	(17.6)	5.3 (−2.2 to 14.8)	0.168	1.39 (0.87 to 2.21)	1.35 (0.84 to 2.17)
Attended irregularly	276	121	(43.8)	260	70	(26.9)	16.9 (8.8 to 24.7)	< 0.001	2.12 (1.47 to 3.05)	2.18 (1.51 to 3.15)
Attended regularly	119	67	(56.3)	122	47	(38.5)	17.8 (5.2 to 29.6)	0.006	2.06 (1.23 to 3.44)	2.14 (1.25 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 v. 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] Could not be computed for five participants, living outside Portugal.

interventions lacked detail, which precludes direct comparisons, the invitations used in this study were based on automated strategies, with expectedly lower cost.

In our study, the adherence to CC screening was 25% when a written letter was used as invitations strategy, which is less than the previous year estimates. This is probably because the data obtained from the primary health care settings referring to the previous year does not distinguish between the participation in organized screening program and opportunistic invitations. The latter are expected to have a small contribution to the adherence estimated in our study, since the outcomes were assessed only 45 days after the invitation.

4.1. Strengths and limitations

To the best of our knowledge, this is the first population-based RCT, testing a multistep intervention, based on automated and low-cost strategies, as well as automated phone calls for invitation to CC screening. However, some limitations should be discussed. This study included only women aged below 50 years, and therefore our conclusions may not apply to older women, with expectedly more limited digital literacy. However, the daily use of mobile phone is already above 90%, for people older than 49 years in Portugal (Anon., n.d.-b).

Although this was a non-blinded study, the potential for inadequate allocation or differential misclassification of the outcome was low. On the one hand, family doctors only assessed the eligibility of the potential participants and the randomization sequence was generated and implemented by the principal investigator, who did not belong to any of the primary care units involved and did not know the participants. On the other hand, the outcome was assessed by researchers not belonging to the primary care units involved, who manually checked the clinical record of each participant, to determine the adherence status in the index dates.

Nearly half the medical doctors invited did not participate in the study, because they considered not having time available to implement the more demanding steps of the intervention (not addressed in this report).Therefore, large differences between women registered in non-participant primary care units/family physicians and those participating are unlikely to have occurred; these could limit the generalizability of our conclusions, but would not compromise the internal validity. Additionally, if invitation by text messages/automated phone calls is adopted as the standard of care to invite women for CC screening its use will not be dependent on the voluntary participation of the medical doctors.

Women excluded before randomization because they had no mobile phone number registered at the national health services database corresponded to < 3% of the total number of participants, and therefore the potential impact of their exclusion on our conclusions is expectedly small.

5. Conclusion and implications for future practice

The SCAN-Cervical Cancer study showed that automated and customized text messages, phone calls and reminders increase the adherence to CC screening in 13.3%, in relation to the standard of care (written letter). All the interventions tested were operator independent with a low-cost per invitation, contributing to the sustainability of organized screening programs. This strategy may be easily replicated in other settings, since it uses mobile phones that are globally available and highly used.

Contributors

JFM and NL designed the study. JFM, RM, AM were responsible for enrolling primary care units, family doctors and clinical secretaries in the trial. SCAN-CC collaborators recruited study participants and verified their eligibility. JFM and SV collected all the outcomes from the clinical records. JFM conducted the data analysis and drafted the first version of the manuscript with contributions of NL. The first draft was edited by JFM and NL. Minor editing was performed by SV, RM and AM. All authors and collaborators revised and approved the final version of the manuscript.

Funding

This work is supported by the groups of primary health care units involved in the study (*ACeS Porto Ocidental* and *Marão e Douro Norte*) and the *Instituto de Saúde Pública da Universidade do Porto*(ISPUP). The groups of primary care units contribute with the human resources involved in the field work and data collection. The cost of text messages and phone calls are supported by *ACeS Porto Ocidental* and ISPUP. This is an academic trial that is supported both by the academic and the primary care institutions involved. Although the members of the research team belong to these institutions, the latter will not interfere in data analysis, results interpretation and decision to submit the manuscripts for publication.

Competing interests

No organization influenced the authors about the decision to submit for publication the current work; there are no financial relationships with any organizations that might have an interest in the submitted work in the previous five years; no other relationships or activities have influenced the submitted work. All the authors declare that they have no competing interests.

Ethics approval

Approved by the Portuguese regional ethics committee – Comissão de Ética da Administração Regional de Saúde do Norte (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). We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

Trial registration number

NCT03122275 (ClinicalTrials.gov).

Study protocol

Study protocol was previously published and can be accessed (Firmino-Machado et al., 2017).

Transparency declaration

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

Appendix A. Definition and calculation of outcomes and process indicators

Outcome/Indicator			Calculation	Index date for outcome assessment
Adherence to screening after text message/phone call *	Numerator	ITT	Number of women screened after being invited through a text message/automated phone call, among those assigned to the intervention group (ρ)	Day after the scheduled appointment†
		PP_1	Number of women screened, among those who picked up the phone call/to whom a text message was delivered ($\chi+\omega+\lambda+\mu+\nu+\xi+o$)	
		PP_2	Number of women screened, among those who confirmed the appointment through text message or automated phone call ($\mu+\nu+\xi+o$)	
	Denominator	ITT	Number of women assigned to the intervention group (β)	
		PP_1	Number of women who picked up the phone call or to whom a text message was delivered ($\theta+\zeta+\eta+\phi+\psi$)	
		PP_2	Number of women who confirmed the appointment through text message or automated phone call ($\iota+\kappa+\zeta+\eta$)	
Adherence to screening after text message *	Numerator	ITT	Number of women screened after being invited through a text message, among those assigned to the intervention group ($\xi+o$)	Day after the scheduled appointment†
		PP_1	Number of women screened, among those to whom a text message was delivered ($\xi+o$)	
		PP_2	Number of women screened, among those who confirmed the appointment through text message ($\xi+o$)	
	Denominator	ITT	Number of women invited through a text message (β)	
		PP_1	Number of women to whom an invitation text message was delivered (δ)	
		PP_2	Number of women who confirmed the appointment through text message ($\zeta+\eta$)	
Adherence to screening after written letter **	Numerator	ITT	Number of women screened, among those assigned to the control group (π)	Day after the scheduled appointment†
		PP_1	Number of women screened, among those invited through a written letter that was not returned (ϑ)	
		PP_2	Number of women screened, among those invited through a written letter that was not returned and did not unscheduled the appointment (subgroup of ϑ)	
	Denominator	ITT	Number of women assigned to control group (α)	
		PP_1	Number of women invited through a written letter that was not returned (γ)	
		PP_2	Number of women invited through a written letter that was not returned and did not unscheduled the appointment (subgroup of γ)	
Text messages delivered	Numerator		Number of participants to whom a text message was delivered (δ)	Day after the last text message was sent
	Denominator		Number of participants to whom a text message was sent (β)	
Automated phone calls picked up	Numerator		Number of particpants who picked up the phone call (θ)	Day after the last phone call was performed
	Denominator		Number of particpants to whom a phone call was attempted (ε)	
Written letters successfully delivered	Numerator		Number of not returned written letters (γ)	Two months after the written letter was sent
	Denominator		Number of letters sent (α)	

ITT - intention-to-treat; PP - per-protocol. PP1 refers to a per-protocol analysis of women to whom a cervical cancer screening invitation was delivered. PP2 refers to a per-protocol analysis of women who confirmed the appointment. *Comparison between intervention and control, regarding the primary objective. **Comparison between intervention and control, regarding the secondary objective; both for the intervention based on text messages + phone calls and the simpler intervention based on text messages alone, adherence to cervical cancer screening was compared with the adherence after written letter invitation. †The index dates were the appointment dates initially proposed or the new dates established after rescheduling the appointment. See further details about Greek letters in Fig. 3.

Appendix B. Per-protocol analyses for the comparison between intervention and control groups, according to age, health care area, deprivation and previous participation in organized screening

	Intervention		Control		% Difference			Crude OR	Adjusted† OR
	n	$n_{adherent}$ (% adherence)	n	$n_{adherent}$ (% adherence)	(95% CI)		p-value*	(95% CI)	(95% CI)
Per-protocol analysis of adherence: among women who received the invitation (intervention – message or phone call successfully delivered; control – written letter not returned)									
All women	517	222 (42.9)	609	158 (25.9)	17.0	(11.5 to 22.4)	<0.001	2.14 (1.67 to 2.76)	2.14 (1.66 to 2.77)
Age (years)									
25-34	256	97 (37.9)	315	83 (26.4)	11.5	(3.9 to 19.1)	0.003	1.71 (1.20 to 2.43)	1.69 (1.18 to 2.42)
35-49	261	125 (47.9)	294	75 (25.5)	22.4	(14.4 to 30.0)	<0.001	2.68 (1.88 to 3.84)	2.73 (1.90 to 3.94)
Health Care Area									
Porto Ocidental	383	173 (45.2)	463	121 (26.1)	19.0	(12.6 to 25.3)	<0.001	2.33 (1.74 to 3.11)	2.28 (1.70 to 3.05)
Marão e Douro Norte	134	49 (36.6)	146	37 (25.3)	11.2	(0.4 to 21.8)	0.042	1.70 (1.02 to 2.84)	1.76 (1.04 to 2.97)
Deprivation of the place of residence ††									
Least deprived	223	93 (41.7)	291	70 (24.1)	17.7	(9.5 to 25.6)	<0.001	2.26 (1.55 to 3.30)	2.17 (1.47 to 3.20)
Intermediately deprived	130	51 (39.2)	143	37 (25.9)	13.4	(2.3 to 24.1)	0.018	1.85 (1.11 to 3.09)	1.84 (1.10 to 3.09)
Most deprived	162	78 (48.1)	175	51 (29.1)	19.0	(8.6 to 28.9)	<0.001	2.26 (1.44 to 3.54)	2.27 (1.43 to 3.60)
Previous participation in organized screening and frequency of attendance									
Never attended	175	45 (25.7)	230	41 (17.8)	7.9	(-0.2 to 16.1)	0.054	1.60 (0.99 to 2.58)	1.51 (0.92 to 2.47)
Attended irregularly	235	114 (48.5)	257	70 (27.2)	21.3	(12.7 to 29.4)	<0.001	2.52 (1.73 to 3.66)	2.55 (1.75 to 3.73)
Attended regularly	107	63 (58.9)	122	47 (38.5)	20.4	(7.4 to 32.4)	0.002	2.29 (1.34 to 3.88)	2.29 (1.32 to 3.97)
Per-protocol analysis of adherence: among women who confirmed the appointment (Intervention – reply to the text message or automatic phone call; control – written letter not returned and appointment not unscheduled)									
All women	306	184 (60.1)	609	158 (25.9)	34.2	(27.5 to 40.5)	<0.001	4.31 (3.22 to 5.76)	4.19 (3.12 to 5.64)
Age (years)									
25-34	137	79 (57.7)	315	83 (26.3)	31.3	(21.5 to 40.5)	<0.001	3.81 (2.50 to 5.80)	3.71 (2.42 to 5.70)
35-49	169	105 (62.1)	294	75 (25.5)	36.6	(27.4 to 45.0)	<0.001	4.79 (3.19 to 7.19)	4.69 (3.10 to 7.09)
Health Care Area									
Porto Ocidental	228	145 (63.6)	463	121 (26.1)	37.5	(29.8 to 44.5)	<0.001	4.94 (3.51 to 6.93)	4.69 (3.32 to 6.63)
Marão e Douro Norte	78	39 (50.0)	146	37 (25.3)	24.7	(11.4 to 37.2)	<0.001	2.95 (1.65 to 5.26)	3.08 (1.68 to 5.62)
Deprivation of the place of residence									
Least deprived	127	71 (55.9)	291	70 (24.1)	31.9	(21.7 to 41.4)	<0.001	4.00 (2.57 to 6.23)	3.94 (2.49 to 6.63)
Intermediately deprived	76	44 (57.9)	143	37 (25.9)	32.0	(18.4 to 44.3)	<0.001	3.94 (2.19 to 7.10)	3.97 (2.19 to 7.20)
Most deprived	103	69 (67.0)	175	51 (29.1)	37.9	(25.9 to 48.3)	<0.001	4.93 (2.92 to 8.34)	4.59 (2.69 to 7.84)
Previous participation in organized screening and frequency of attendance									
Never attended	77	35 (45.5)	230	41 (17.8)	27.6	(15.7 to 39.5)	<0.001	3.84 (2.19 to 6.74)	3.67 (2.04 to 6.61)
Attended irregularly	161	100 (62.1)	257	70 (27.2)	34.9	(25.3 to 43.6)	<0.001	4.38 (2.88 to 6.67)	4.40 (2.88 to 6.74)
Attended regularly	68	49 (72.1)	122	47 (38.5)	33.5	(18.9 to 45.9)	<0.001	4.12 (2.16 to 7.83)	4.29 (2.18 to 8.44)

CI - Confidence Interval. *Comparison between intervention and control; †Adjusted for age (continuous), education (< 9, 9–12, 12, > 12 years), household size (≤ 2 vs. > 2 people), employment status (student/employed v. 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); ††Deprivation index could not be computed for two participants who had place of residence outside Portugal.

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3.3 Paper III

Firmino-Machado J, Mendes R, Moreira A, Lunet N. Translating evidence into practice: insights on the reporting of trial results to health professionals and institutions (submitted).

Title: Translating evidence into practice: insights on the reporting of trial results to health professionals and institutions

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Funding

This an academic study, supported by the institutions to which authors are affiliated, but with no specific funding.

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Short title: Communication of RCT findings

Word count

Full body: 1200 words

Type of article

Perspective

Title: Translating evidence into practice: insights on the reporting of trial results to health professionals and institutions

Keywords: Randomized Controlled Trial; Mass Screening; Translational Medical Research; Information Dissemination; Health Communication.

INTRODUCTION

The communication of results from public health interventions to the professionals involved in their implementation and evaluation is an important component of research in this field, and is essential to have the support of health professionals who will be involved in their implementation and evaluation.[1] In addition to academic publications and presentations in scientific fora, this requires the communication of results using multiple means, to reach different targets, including easy-to-read reports directed to broad audiences.[2]

Some strategies that promote an effective communication of results have been described, such as tailoring the message to include information that is specific for each individual/institution or selecting the most relevant results for each audience segment.[3]

PROPOSED FRAMEWORK

Here we propose a framework to report the main findings of experimental studies to health institutions and professionals involved in the assessment of the effectiveness of an intervention, based on the trial *Stepwise strategy to improve Cervical Cancer Screening Adherence (SCAN-Cervical Cancer)*, which was previously described in detail elsewhere.[4,5] This study tested the invitation to cervical cancer screening through automated and personalized text messages, phone calls and reminders to increase the adherence to cervical cancer screening, in relation to the standard of care (written letter). The participants were women eligible for cervical cancer screening, aged 25 to 49 years, registered at one of the 13 participant primary care units, including urban and rural areas (Figure 1 of the Appendix), with an available mobile phone registered at the National Health Service database. The primary outcome was the adherence to screening 45 days after implementing the interventions.

We produced a two-page template (please see Appendix) to disseminate the evidence produced by a pragmatic randomized controlled trial to the involved health professionals and institutions. It comprises the description of the study rationale, design of the trial, settings and participants, interventions, results of the study, discussion of the internal and external validity, summary of main findings, as well as funding and conflict of interest. A detailed analysis of each section is presented in Box 1.

Box 1 – Template proposed to communicate the main findings of experimental studies.

1| Rationale for the investigation

Identification, magnitude and relevance of the problem to be tackled with the intervention. This section should also identify the knowledge gaps addressed by the investigation.

2| Study description

2.1 – Objective and study design

Objective of the investigation and study design details, such as number of centers, randomization units, blinding and other methodological features with potential impact on internal and external validity.

2.2 – Settings and participants

Inclusion and exclusion criteria, as well as the characteristics of the areas/institutions involved in the study. This information can be communicated using plain text, but also graphical representations, such as flowcharts or diagrams (*e.g.*, CONSORT diagram). Maps can also be used to depict the geographical distribution of the recruiting sites (*e.g.*, Figure 1 of the appendix).[6]

2.3 – Tested intervention and control

Tested intervention and comparator, and study implementation. Flowcharts, process content diagrams or swim lane activity diagrams may be useful to improve the understanding of complex study interventions.[7] These graphical elements may be particularly useful when the study designs are complex (e.g., Figure 2 of the Appendix).

3| Results of the trial

3.1 – Overall effect of the intervention.

Overall results of the intervention can be presented using different effect measures, along with precision estimates (*e.g.*, 95% confidence intervals), and p-values for comparisons between intervention and control groups.

Measures such as the number needed to treat (NNT), as these are easily interpreted by clinicians and illustrate the number of patients that need to be treated to prevent one adverse outcome. NNT can also be adapted to address different research topics, namely vaccination (number needed to vaccinate) or screening (number needed to screen).

3.2 – Effect of the intervention by recruiting site and population subgroups.

Effect estimates stratified by recruiting sites, for benchmarking of results.

Funnel or forest plots may be used to depict strata-specific results. Funnel plots are commonly used to access publication bias in meta-analyses, but they can also be used to depict the heterogeneity of effect measures across study centers.[8]

This format of graphic display of the results avoids the use of confidence intervals, though instructions for a proper interpretation of the funnel plots may be needed (e.g., Figure 3 of the Appendix). Forest plots could be used instead, for graphical presentation of center-specific data, as well as to depict the effect of the intervention stratified by any relevant baseline characteristic, namely sociodemographic variables or presence of comorbidities (e.g., Figure 4 of the Appendix), enabling the identification of participants sub-group(s) in which the intervention is more/less beneficial.

4| Internal and external validity

4.1 – Internal validity

Threats to the internal validity of the study should be addressed in this section and may comprise topics such as imbalance of participants baseline characteristics between intervention and control groups, contamination, differential losses to follow-up or misclassification of the outcome, among others.

4.2 – External validity

The limits to the generalizability of study findings, i.e. "the degree to which results of a study may apply, be generalized, or be transported to populations or groups that did not participate in the study" [9], along with the extent to which the trial may be considered pragmatic should be addressed.

A more comprehensive and systematic assessment of the pragmatic nature of the trial may be achieved using tools such as the PRagmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2).[10]

5| Summary of main findings

The summary of the main findings may be complemented by a statement on the potential applicability or usefulness of the intervention in the specific setting being targeted by the report.

6| Funding and conflict of interest

All project grants or supporting funds of the research project should be presented, so as any conflict of interest of the research team, as defined by the International Committee of Medical Journal Editors (ICMJE).

USE OF THE PROPOSED TEMPLATE IN SCAN TRIAL

A personalized report was assembled for each primary care unit involved in the trial, using the proposed template. Each document was signed by the principal investigator and sent by e-mail to all the involved health professionals and institutions. The use of a two-page report allowed health professionals to quickly read it but also to print and post it as poster in each primary care unit, promoting the dissemination of findings.

A meeting with the primary care unit was scheduled to discuss the overall results of the trial, but also the effect of the intervention in each recruiting site. The same presentation was conducted with the coordinators of the primary care units involved.

Through these strategies we have promoted the discussion and dissemination of the study results to the involved health professionals and possibly contributed to a sustainable implementation of the tested intervention.

In conclusion, this two-page template can be easily customized according to the intended audience. This work may be useful to disseminate study findings of experimental studies, although further research is needed to quantify the acceptance of the proposed template by different groups of health professionals (medical doctors, nurses, health managers) and types of institutions (primary health care units, hospitals), but also to determine which is the most effective strategy to disseminate findings of distinct nature.

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Contributions of authorship

JFM and NL designed the study. JFM, RM, AM were responsible for enrolling primary care units, family doctors and clinical secretaries in the trial. JFM collected all the data necessary for data analysis. NL conducted the data analysis with inputs from JFM. The proposed template was produced by JFM and presented to primary care units health professionals and policy makers by JFM, RM and AM. The first version of the manuscript was drafted by JFM and edited by NL. All authors revised and approved the final version of the manuscript. The lead author affirms that the manuscript is an honest, accurate, and transparent and is accountable for all the aspects of the work.

Conflict of interests

All the authors declare that they have no competing interests.

APPENDIXES

Appendix 1 - Template to disseminate the evidence produced by a randomized controlled trial to the involved health professionals and institutions.

Stepwise strategy to improve cervical cancer screening adherence (SCAN-Cervical Cancer)

Report for: *USF Espaço Saúde*

1| Rationale for the investigation

Cervical cancer is the fifth most common cause of cancer death in women (Portugal), and organized screening programs are important for its prevention and control. However, the population adherence in *Porto Ocidental* is just over 30%. The previously described interventions that intended to increase the adherence to cervical cancer screening targeted essentially hard-to-reach women and did not test low-cost or automated strategies.

2| Study description

Objective: to assess the effectiveness of a novel strategy to invite women for cervical cancer screening.

Study design: randomized controlled trial (pragmatic design, 12 centres, randomization of individuals).

Inclusion criteria:

- Women eligible for cervical cancer screening
- Age 25 to 49 years
- Registration at one of the participant primary care units (Figure 1.A and 1.B)
- Mobile phone number available at the National Health Database

Tested intervention: invitation based on automated and personalized text messages/phone calls and reminders (Figure 2).

Control: invitation through written letter (standard of care).

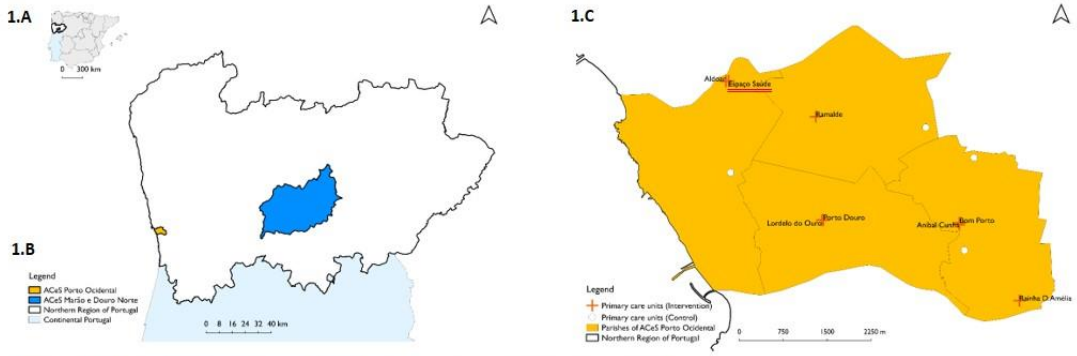

Figure 1 – Map of the participant health care areas and primary care units.
ACeS – Agrupamento de Centros de Saúde. The participant health care areas are depicted in Figure 1.A and 1.B. The enrolled primary care units of *ACeS Porto Ocidental* are represented in Figure 1.C. ACeS Porto Ocidental serves a urban area, while ACeS Marão e Douro Norte covers a sub-urban and rural territory.

Figure 2 – Flowchart depicting the implementation of the intervention.

3| Results of the trial

Overall effect of the intervention

On an intention-to-treat analysis, the adherence to cervical cancer screening was significantly higher among women assigned to intervention than to control group (39.0% vs. 25.7%, p<0.001), corresponding to a difference of 13.3% (95% Confidence Interval [95% CI] 8.1 to 18.5), an Odds Ratio (OR) of 1.85 (95% CI 1.45 to 2.37) and a number needed to screen of 8.

Effect of the intervention by recruiting site and population subgroups

The superiority of the intervention was homogeneous across all the participant primary care units (Figure 3).

For USF Espaço Saúde the adherence was 22.2% in the intervention and 19.5% in the control groups, corresponding to a difference of 3.4% (95% CI -10.5 to 17.3) and an OR of 1.17 (95% CI 0.61 to 2.25).

The effectiveness of the intervention was higher among women aged 35-49 years, living in a more deprived area and among those who participated previously in organized screening (Figure 4).

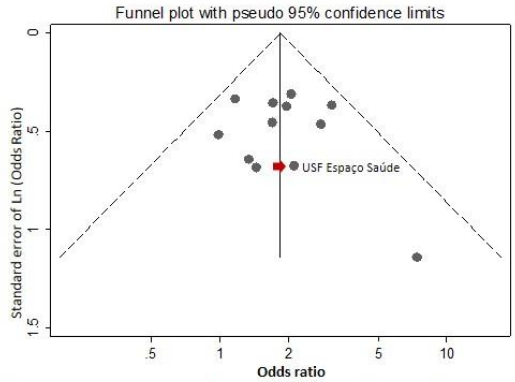

Figure 3 – Funnel plot* representing the odds ratios for the association between the intervention and adherence to cervical cancer screening, across the primary care units involved.

*Dots represent each of the participant primary care units (PCU). The vertical line depicts the overall effect. Results from each PCU are significantly different from the overall effect only when falling outside the triangle defined by the dashed lines.

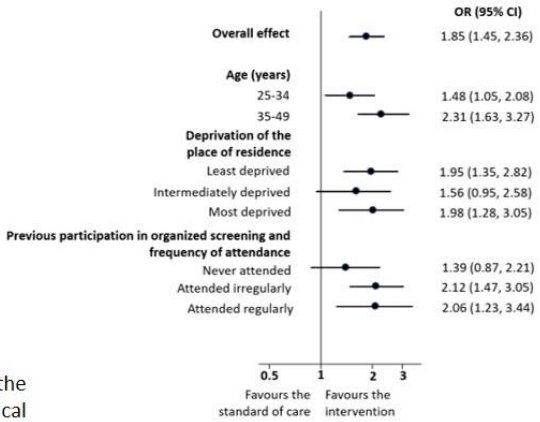

Figure 4 – Forest plot representing the effect of the intervention stratified by age group, deprivation and previous participation in organized screening.

4| Internal and external validity

Internal validity: this investigation was based on a robust study design, and no major threats to the internal validity were identified.

External validity: this trial only included women aged 25 to 49 years, although cervical cancer screening is recommended till 65 years; therefore, the conclusions may not apply to older women, with expectedly more limited digital literacy. The proposed intervention was tested in health care units with characteristics similar to the primary health care settings that may be targeted by this intervention, and was tailored to the specificities of each center. The recruitment and follow-up procedures have replicated the standard practice in each center.

5| Summary of main findings

A strategy based on automated and customized text messages, phone calls and reminders increased the adherence to cervical cancer screening in 13.3%, in relation to the standard of care (written letter). For USF Espaço Saúde, the proposed intervention increased the adherence in 3.4%. This invitation strategy is operator-independent, and therefore has the potential to be easily implemented on a regular basis.

6| Funding and conflict of interest

This was an academic study supported by the institutions involved: *Instituto de Saúde Pública da Universidade do Porto*, *ACeS Porto Ocidental* and *ACeS Marão e Douro Norte*. The authors have no conflict of interest to declare.

For further information contact: [phone number] | [institutional e-mail]

3.4 Paper IV

Firmino-Machado J, Varela S, Mendes R, Moreira A, Lunet N. A 3-step intervention to improve adherence to cervical cancer screening: the SCAN randomized controlled trial. Prev Med. 2019;123:250-261.

Preventive Medicine 123 (2019) 250–261

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

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

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ARTICLE INFO

Keywords:
Mass screening
Early detection of cancer
Uterine cervical neoplasms
Text messaging
Reminder systems

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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https://doi.org/10.1016/j.ypmed.2019.03.025
Received 7 August 2018; Received in revised form 6 February 2019; Accepted 16 March 2019
Available online 30 March 2019

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

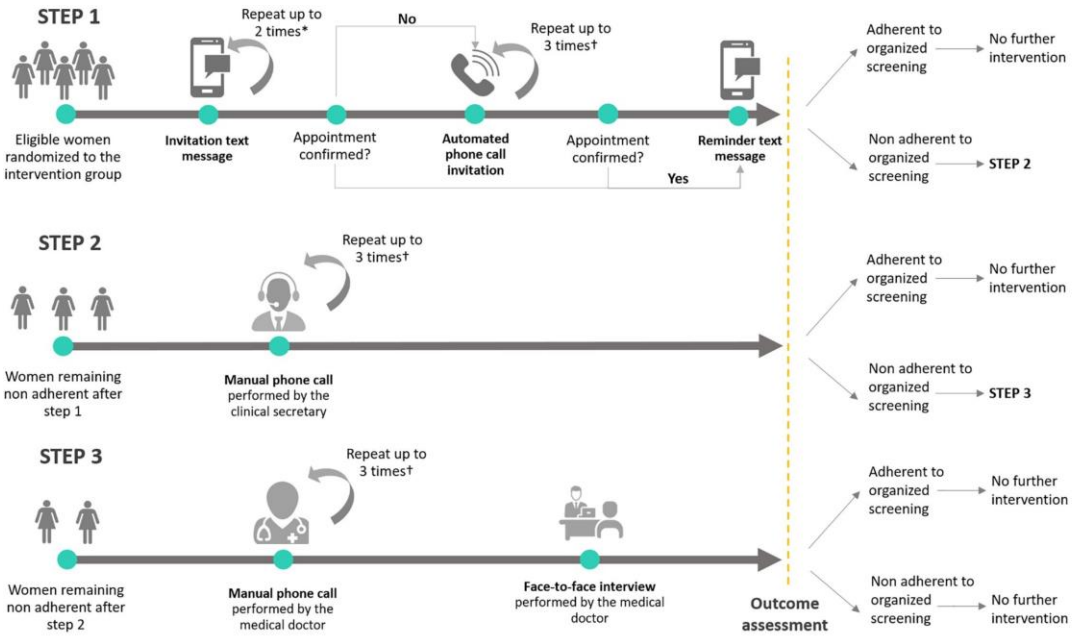


Fig. 1. Description of the intervention.
*When a text message was not delivered successfully a new attempt was performed on the following day. †When a connection was not established, a new phone call was performed on the following day, for a maximum of three days.

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

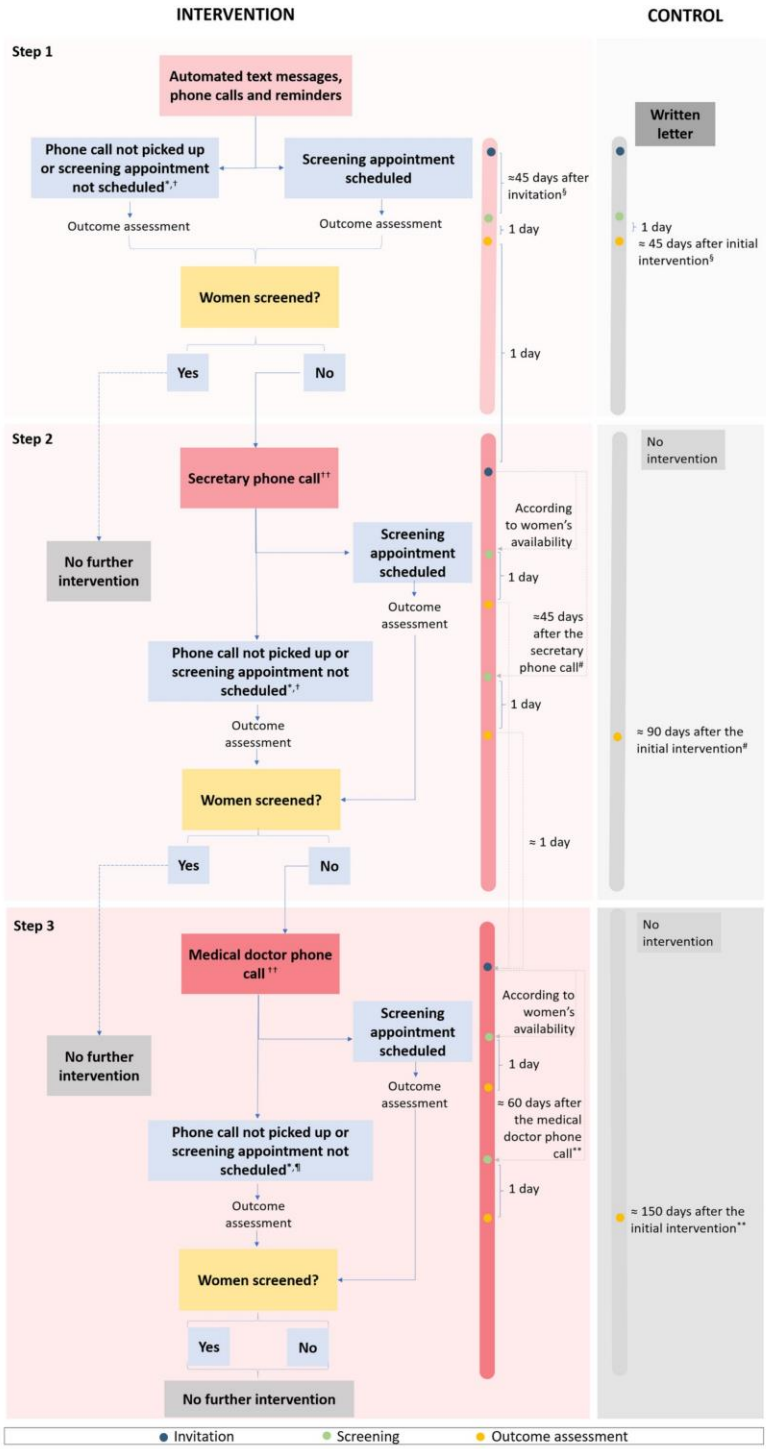


Fig. 2. Implementation of the intervention, timing of invitation for cervical cancer screening and index dates for outcome assessment.
*Women not scheduling a screening appointment within the screening program could undergo opportunistic screening. †Women were asked to provide the reason for not scheduling 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

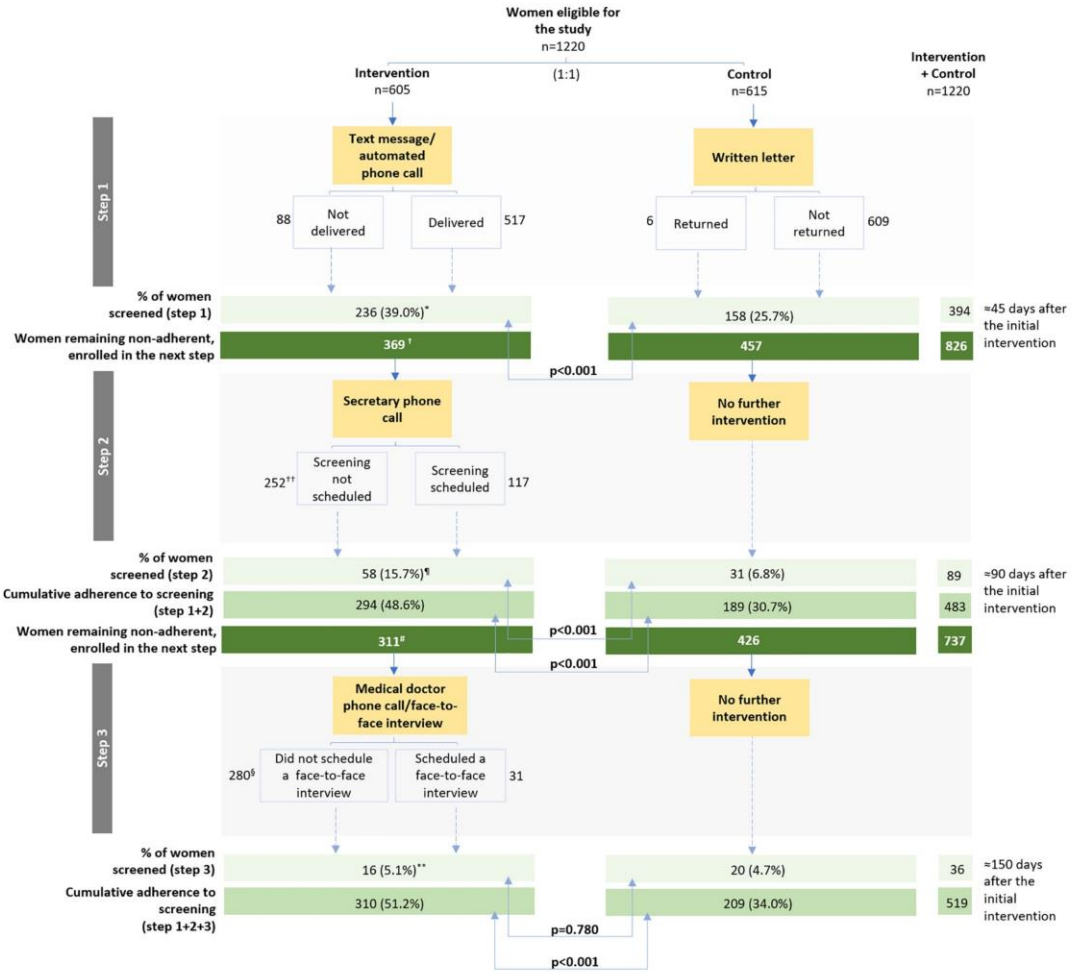


Fig. 3. Delivery of invitations and adherence to screening among intervention and control groups.
*Includes 14 women who were screened despite text messages/automated phone calls were not delivered. †For 31 women an exclusion criterion was identified before implementing step 2: prior cervical cancer (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.

Funding

This work was supported by *ACeS Porto Ocidental*, *ACeS Marão e Douro Norte* and the *Instituto de Saúde Pública, Universidade do Porto* (ISPUP). The groups of primary care units contributed with the human resources involved in the field work and data collection. The cost of text messages and phone calls were supported by *ACeS Porto Ocidental* and ISPUP.

Authors' contributions

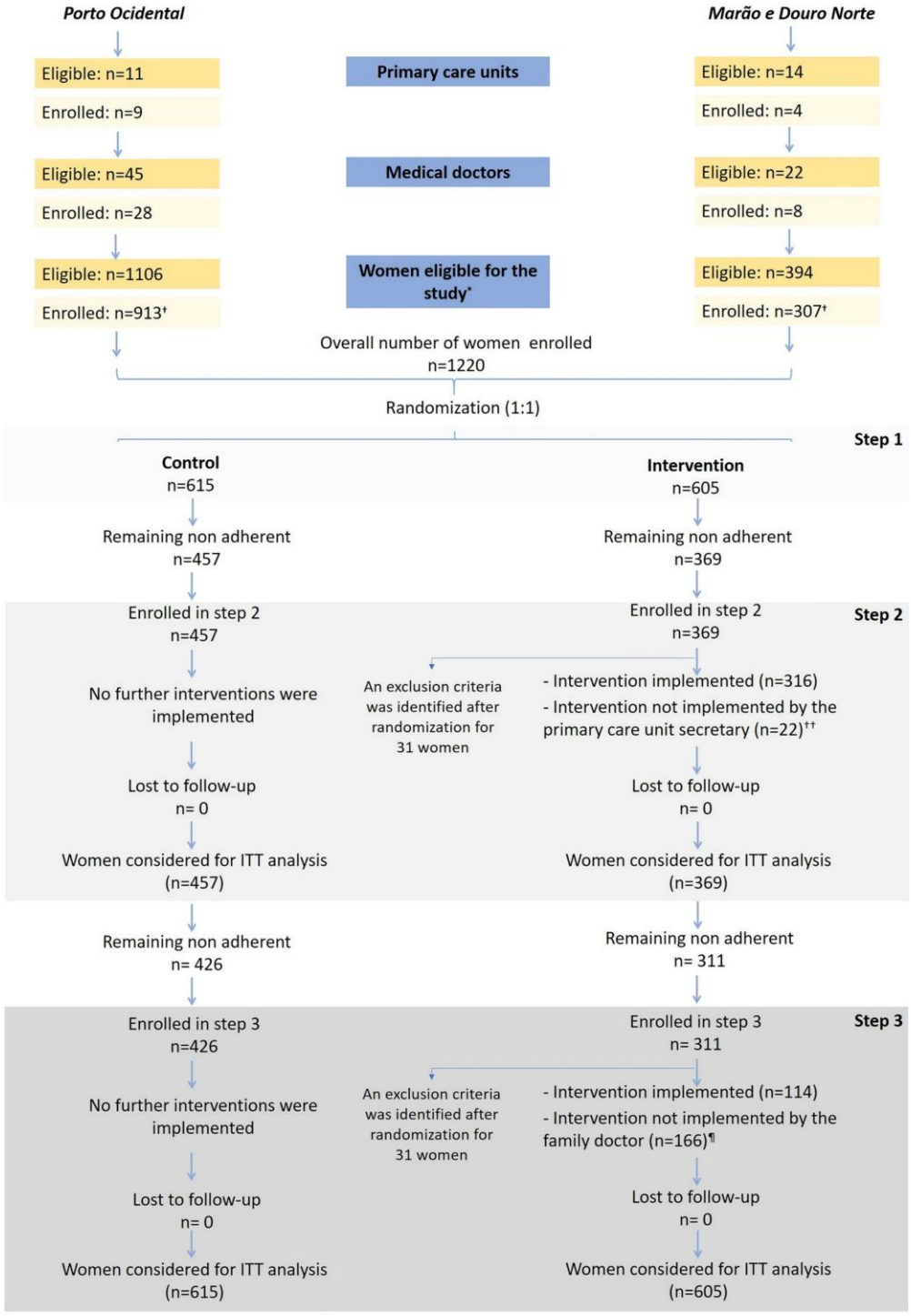
JFM and NL designed the study. JFM, RM, AM enrolled the recruiting sites, family doctors and clinical secretaries in the study. SCANCC collaborators recruited the study participants and verified their eligibility. JFM and SV collected the study and study variables from the medical records. JFM conducted 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.

Acknowledgements

SCAN-Cervical Cancer collaborators:

Alexandra Carmo, Ana Cancela, Ana Firmino, Ana Ramos, Antonieta Teixeira, Armando Vieira, Bárbara Badim, Carolina Tojal, Cláudia Junqueira, Conceição Pinheiro, Emília Peneda, Helena Monte, Hugo Marcelo Vieira, Inês Proença, Joana Seabra, Joana Teixeira, João Magalhães, Joaquim Batista, Justina Silva, Leonor Grijó, Liliana Beirão, Manuela Castanheira, Margarida Silva, Maria João Peixoto, Marina Ponto Santos, Mariana Neves, Miguel Amaral, Nuno Capela, Paulo Santos, Pedro Apolinário, Rita Aguiar, Rita Barbosa, Rui Amendoeira, Rui Medon, Sofia Pinheiro Torres, Sofia Varela, Susana Silva, Tiago Fernandes, Vítor Santos.

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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3.5 Paper V

Firmino-Machado J, Soeteman D, Lunet N. Cost-effectiveness of a stepwise intervention to promote adherence to cervical cancer screening (submitted).

Cost-effectiveness of a stepwise intervention to promote adherence to cervical cancer screening

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Word count: Abstract: 234; Main text: 2353

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ABSTRACT

Background

Cervical cancer screening is effective in reducing mortality, but adherence is generally low. We aimed to investigate the cost-effectiveness of a stepwise intervention to promote adherence to cervical cancer screening in Portugal.

Methods

We developed a decision tree model to compare the cost-effectiveness of four competing interventions to increase adherence to cervical cancer screening: (a) a written letter (standard of care); (b) automated short message service text messages (SMS)/phone calls/reminders; (c) automated SMS/phone calls/reminders + manual phone calls; (d) automated SMS/phone calls/reminders + manual phone calls + face-to-face interviews. The main outcome measure was cost per quality-adjusted life year (QALY) measured over a 5-year time horizon. Costs were calculated from the societal and provider perspectives.

Results

From the societal perspective, the optimal strategy was automated SMS/phone calls/reminders, below a threshold of €9394 per QALY; above this and below €172339 per QALY, the most cost-effective strategy was automated SMS/phone calls/reminders + manual phone calls and above this value automated SMS/phone calls/reminders + manual phone calls + face-to-face interviews. From the provider perspective, the ranking of the three strategies in terms of cost-effectiveness was the same, for thresholds of €4286 and €167230 per QALY, respectively.

Conclusions

Assuming a willingness-to-pay threshold of one time the national gross domestic product (€22398 /QALY), automated SMS/phone calls/reminders + manual phone calls is a cost-effective strategy to promote adherence to cervical cancer screening, both from the societal and provider perspectives.

Key Words

Cost Effectiveness; Cervical Cancer; Mass Screening; Patient Adherence; Decision Trees; Economic Models.

INTRODUCTION

Cervical cancer is the fourth most commonly diagnosed cancer and cause of cancer death in women globally, estimated to account for more than 310 000 deaths per year.[1] A substantial part of the cases of cervical cancer can be prevented by human papillomavirus (HPV) vaccination and screening.[2,3] The latter has been proven effective in decreasing cause-specific mortality, potentially up to 80%, and will remain necessary even with widespread HPV vaccination, to cover non-vaccinated women.[4] However, the sustainability of cervical cancer screening programs requires more cost-effective approaches, since the participation in organized screening is often low and HPV vaccination will decrease the number of eligible women.[5]

The effectiveness of many different strategies to increase adherence to cervical cancer screening was previously investigated against the standard of care (usually written invitation letter), including the use of patient reminders, brochures and videos and face-to-face interviews performed by health professionals or researchers.[6] However, previous reports often lack detailed cost information about the interventions tested, precluding a comprehensive cost-effectiveness analysis.[7–12]

Stepwise interventions using automated and inexpensive invitation strategies for the entire eligible population and increasingly customized and expensive methods only for non-adherent women, may provide an affordable solution to promote adherence to cervical cancer screening. The aim of this study was to compare the cost-effectiveness of a stepwise invitation strategy designed to increase adherence to cervical cancer screening compared with the standard of care (a written invitation letter), using a disease simulation model, developed with patient-level data and data from the published literature.

METHODS

We estimated the cost-effectiveness of the interventions previously evaluated in the Stepwise Strategy to improve Cervical Cancer Screening Adherence (SCAN) study.[13,14] This is a multicentre, parallel, population-based randomized controlled trial that aimed to investigate the effectiveness of different strategies to increase adherence to cervical cancer screening in Portugal. It included a total of 1220 women eligible for cervical cancer screening aged 25 to 49 years. Women who were randomized to the control group (n=615) were invited by a written letter (*i.e.*, standard of care) and those randomized to the intervention group (n=605) were invited through automated short message service text messages (SMS)/phone calls/reminders; the invitation strategy included also manual phone calls and face-to-face interviews, applied sequentially to women remaining non-adherent.

The SCAN trial was approved by the regional ethics committee – Comissão de Ética da Administração Regional de Saúde do Norte (reference: 20/2017) – and by the National Data Protection Committee (reference: 11467/2016).

Model Overview

To estimate the impact of the tested interventions on outcomes measured over a 5-year time horizon, including cost per quality-adjusted life year (QALY), cost per death avoided and cost per woman screened, we developed a decision tree model that integrated primary data from the SCAN trial and published data.

Based on the SCAN trial, we defined four competing interventions for our cost-effectiveness model (Figure 1), as follows: (a) invitation through written letter; (b) invitation through automated SMS/phone calls/reminders; (c) invitation through automated SMS/phone calls/reminders + manual phone calls performed by a primary care unit secretary; and (d) invitation through automated SMS/phone calls/reminders + manual phone calls performed by a primary care unit secretary + face-to-face interview performed by a medical doctor.

Regardless of the strategy used, women adherent to cervical cancer screening could have a positive or negative screening test result. Participants who tested positive could have no cervical lesion or be diagnosed with a precancerous lesion or cervical cancer. Women testing negative could have no cervical lesion, or have a precancerous lesion or cervical cancer that remains undetected. Women with a precancerous lesion (detected or not during screening) were considered to survive for at least five years. Cancer-specific survival estimates were used to define the probability of women with a cervical cancer (identified or not during screening)

surviving during the 5-year time horizon of the model.[15–18] The model was implemented in TreeAge Pro 2017.[19]

Health benefits

The health benefits considered in the decision model are summarized in Table 1 and their calculation is detailed in Appendixes 1 and 2. Adherence to cervical cancer screening was estimated using data from the SCAN trial, at 34.0% for strategy (a), 43.0% for strategy (b), 50.6% for strategy (c) and 51.2% for strategy (d).[13,14]

The implementation of strategies (b), (c) and (d) is dependent on the quality of mobile phone number registers, which is heterogeneous across primary care units. Therefore, we have assumed a probability of successful delivery of automated SMS/phone calls/reminders of 80.7% (overall estimate of the SCAN trial) in our base case and varied this parameter between 68% and 85% in a sensitivity analysis; this range corresponds to the minimum and maximum values observed across the different recruiting sites in the SCAN trial.[14]

The 5-year relative survival estimates and utility values assigned to each health state of the decision model were obtained from previously published studies. Women with a cervical cancer were considered to have a 5-year relative survival of 0.893 if previously tested positive on the screening test; 0.795 if previously tested negative on the screening test (*i.e.*, false negatives); 0.754 if were non-adherent to organized screening program. [15–18] All participants with a pre-cancerous lesion or with no abnormal findings in the cytology were considered to be alive after 5-years. The survival estimates may be influenced by the cervical cancer epidemiology and organization of the health services, which are different in each country. Therefore, the parameters were varied in plus or minus 10% in the sensitivity analysis, because these were not locale-specific data.

Utility values for the different health states (i.e., false positive screening test, precancerous lesion, cervical cancer survivorship or death) ranged from a minimum of 0 to a maximum of 1, representing a health state that equals death and perfect health, respectively. Women had no disease but who tested positive on a screening test, *i.e.* the false positives, were considered to have a utility value of 0.9967 for a one-year period, and 1 thereafter.[20] Women with a precancerous lesion were considered to have a utility of 0.9704 during one year and a utility of 1 after that period.[21] Those with cervical cancer, detected during screening or otherwise, who survived after treatment were considered to have a utility value of 0.715 for a 5-year period. Those who died from a cervical cancer, detected during screening or otherwise, were assigned a utility of 0, over the 5-year period.[22] Women without cancer and no abnormal findings during screening were assigned a utility value of 1.[23]

Future benefits were discounted at a rate of 3% annually, based on the World Health Organization recommendations.[24]

Costs

Costs were calculated from the provider perspective, which includes the costs incurred by a health institution when providing a health service, and from the societal perspective, which additionally includes the costs incurred by the women to access the service. All future costs were discounted at a rate of 3% annually.[24] A summary of the costs considered in the decision tree models is provided in Table 1 and the calculation details are described in Appendixes 3 (costs of the tested interventions) and 4 (costs of cervical cancer screening, curative treatment and end of life care). The costs incurred by the health institutions included those related with: women invitation to screening, screening test, workout of a positive screening test, curative treatment of cervical cancer and end-of-life care costs. The costs incurred by the women included those due to travel expenses, productivity losses because of cervical cancer and travel time to screening and all the required medical treatments. In the sensitivity analysis we considered 20% smaller costs of workout of a positive screening test, cervical cancer curative treatment and end-of-life care, because these estimates were obtained from countries with higher gross domestic product (Appendix 3). Fixed costs related with the infrastructure were assumed to be the same between all invitation strategies and were therefore not considered in data analysis.

An additional analysis was conducted considering only short-term costs, which comprise the invitation costs but do not include those related to screening and treatment and considering as outcome the cost per women screened.

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) was calculated as the additional costs divided by the additional health benefits of one strategy compared to the next less-costly strategy. The ICERs was compared to an external willingness-to-pay (WTP) threshold to identify the most cost-effective invitation strategy. The strategy that has the highest ICER just below the threshold is considered the invitation strategy that provides the most health benefit considering a budget constraint, *i.e.* the most cost-effective option.

RESULTS

The 5-year costs and benefits, and cost effectiveness results are presented in Table 2, and detailed results from the sensitivity analysis are depicted in Table 3.

5-year costs and benefits

From the provider perspective, the total 5-year mean cost per woman invited ranged from a minimum of 22.7€ for strategy (b), to a maximum of 24.4€ for strategy (d). The short-term cost analysis, *i.e.*, including only invitation costs, yielded a mean cost per women invited ranging from a minimum of 0.1€, for strategy (b), to a maximum of 2.7€, for strategy (d). From the societal perspective, the total 5-year mean cost per woman invited was lowest for strategy (b) and highest for strategy (d), at 25.7€ and 27.9€ per women invited, respectively. The short-term mean cost was also lowest for strategy (b) and highest for strategy (d), at 3.1€ and 6.2€ per women invited, respectively.

Regarding QALYs, strategy (a) was the least effective, with 4.6076 QALYs per women invited over a 5-year period, and strategy (d) was the most effective, with 4.6078 QALYs per women invited. The pattern was similar for the mean number of avoided deaths, with strategy (a) being the least effective (0.999910 avoided deaths per women invited) and (d) as the most effective (0.999930 avoided deaths per women invited). In terms of adherence to organized screening, the least effective strategy was the standard of care (strategy a) and the most effective was strategy (d), at 34.0% and 51.2%, respectively.

Cost-effectiveness results

From the provider perspective, strategy (a) was eliminated, because it was strongly dominated by strategy (c), *i.e.*, it was costlier and less effective. The ICER was 4286€ per QALY and 167230€ per QALY for strategies (c) and (d), respectively. From the societal perspective, strategy (a) was strongly dominated by strategy (b) and thus eliminated from the analysis. Strategy (c) and (d) had ICERs of 9394€ per QALY and 172339€ per QALY, respectively.

One-way sensitivity analysis

The ranking of the interventions and the optimal intervention in terms of cost-effectiveness did not change over the range of parameter values used in sensitivity analysis. Strategy (a) was

consistently (strongly) dominated in all analyses. Strategy (d) was also dominated when considering an increase in adherence over time, due to opportunistic invitations, greater than 3%.

DISCUSSION

The invitation to cervical cancer screening based on automated SMS/phone calls/reminders + manual phone calls was very cost-effective, both from both the societal and provider perspectives. Although at a national level there is no universally-accepted threshold for the WTP for a QALY, we interpreted the results according to the cut-offs commonly applied in cost-effectiveness analyses of one (very cost-effective) and three times (cost-effective) the national gross domestic product per capita (*i.e.*, €22398 and €67194 per QALY in Portugal in 2016).[25]. However, policy makers may have short-term budget constraints that prevent them from adopting the most cost-effective strategy. In this scenario, they should implement an invitation based exclusively on automated SMS/phone calls/reminders, which was the less costly intervention in the short-term, but also more effective than the standard of care.

To the best of our knowledge, this is one of the few studies reporting on a detailed and comprehensive cost-effectiveness analysis of interventions that intend to promote adherence to cervical cancer screening. The major strength of this study is that it considers essentially patient level data, drawn from a methodologically robust randomized controlled trial. The present study also adds to most previous cost-effectiveness analyses on this topic by considering avoided deaths and QALYs as an outcome[7–12] and by estimating costs and benefits from the societal perspective.[7–12] Additionally, model parameter uncertainty was considered by conducting sensitivity analyses[7,8,10,12] and future costs and benefits were discounted over time.[7–10,12]

However, some limitations of our study need to be addressed. First, the adherence to cervical cancer screening considered in the decision tree model was determined among women aged 25 to 49 years, using the SCAN trial, although the remaining transition parameters, which were obtained from previously published studies, refer to women aged 25 to 65 years. However, the conducted sensitivity analysis showed that the conclusions do not change after plausible variations of the transition parameters.

Secondly, strategies (b), (c) and (d) depend on the availability of updated mobile phone numbers on the medical records of the eligible women, both for SMS and manual phone call invitations. Therefore, adherence to cervical cancer screening may be smaller in areas with a lower quality of phone number records. However, the sensitivity analysis showed that strategy (c) will remain the most cost-effective intervention even if the proportion of successfully delivered automated interventions is just below 40%.

Finally, the present study considers a time-frame of five years instead of the complete lifetime of the women invited to cervical cancer screening. Therefore, it does not comprise the potential longer-term benefits due to carry-over effect of these intervention, which are expectedly larger among the invitation strategies that depart from the standard of care. We opted for this type of analysis to allow the use of more reliable parameters, particularly survival estimates, which are usually published for the five years after a pre-malignant or malignant disease.

In conclusion, our study provides robust evidence for policy makers and health managers to define automated SMS/phone calls/reminders + manual phone calls as the new standard of care strategy for women invitation to cervical cancer screening, under a willingness-to-pay threshold of one time the national gross domestic product (€22398 per QALY), or at least to replace a written letter invitation by automated SMS/phone calls/reminders, which was more effective than the standard of care and the less costly intervention in the short-term.

Funding

This project did not receive any specific funding.

Conflict of interest

None declared.

KEY POINTS

• This study uses patient-level data from a randomized controlled trial and data from previously published studies to build a decision-analytic model to assess the cost-effectiveness of interventions aiming to increase the adherence to cervical cancer screening.

• Assuming a willingness to pay of €22398 per QALY, automated SMS/phone calls/reminders + manual phone calls was a cost-effective invitation strategy from both the societal and provider perspectives.

• Invitation using a written letter (standard of care) was costlier and less effective than an invitation based exclusively on automated SMS/phone calls/reminders (societal perspective) or automated SMS/phone calls/reminders + manual phone calls (provider perspective) and therefore cannot be considered a cost-effective intervention.

• These conclusions hold when uncertainty in model parameters was taken into account, including the probability to deliver the interventions, as well as screening and treatment costs.

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TABLES

Table 1 - Summary of decision tree model parameters.

Description of the transition probabilities	Base case (p)	Range	Further details
Probability of adherence to cervical cancer screening after step (a)	0.34		*(please see appendix 2 for probability calculation details)*
Probability of adherence to cervical cancer screening after step (b)	0.43	0.386 - 0.432††	*(please see appendix 2 for probability calculation details)*
Probability of adherence to cervical cancer screening after step (c)	0.506	0.449 - 0.508††	*(please see appendix 2 for probability calculation details)*
Probability of adherence to cervical cancer screening after step (d)	0.512	0.451 - 0.514††	*(please see appendix 2 for probability calculation details)*
Probability to test positive on the screening test (any type of abnormal finding)	0.0195[1]		Based on data from the assessment report of cervical cancer screening in the North Region of Portugal.
Probability to have a cervical intraepithelial neoplasia grade 2 or over (CIN 2+), among women who tested positive	0.1753[2]		This corresponds to the positive predictive value of the screening test (HPV test+cytology) for a CIN2+ lesion.
Probability to have no abnormal cytology, among women who tested negative on the screening test	0.9979[2]		This corresponds to the negative predictive value of the screening test.
Probability to have cancer among women who tested positive and have a CIN2+ lesion	0.017[3]		The same estimate was assumed for women who tested negative on the screening test and had a CIN2+ lesion.
Probability to have cancer among non-screened women	0.0002[1]		Based on data from the assessment report of cervical cancer screening in the North Region of Portugal. Since the prevalence of cervical cancer is only available for women who adhered to cervical cancer screening, the prevalence among the non-screened was estimated assuming a correction factor,
Probability to have a precancerous lesion among non-screened women	0.0193[1]		It was assumed that the probability to have a precancerous lesion is the same as in the screened population. Data is based on the regular assessment of cervical cancer screening in the North Region of Portugal.
5-year survival probability among women with a confirmed cervical cancer, who previously tested positive on the screening test	0.893[5]		
5-year survival probability among women with a confirmed cervical cancer, who previously tested negative on the screening test	0.795[5]		
5-year survival probability among women with a confirmed cervical cancer, who were not adherent to organized cervical cancer screening	0.754[5]		These women may undergo opportunistic screening.
5-year survival probability among women with a pre-cancerous lesion	1		
5-year survival of a healthy women	1		
Description of cost parameters	**Base case(€)***	**Range**	**Further details**
Invitation letter	0.80		*(please see appendix 3 for cost calculation details)*
Automated text messages/phone calls and reminders			*(please see appendix 3 for cost calculation details)*
Invitation delivered	0.10		
Invitation not delivered	0.05		
Secretary phone call	1.27		*(please see appendix 3 for cost calculation details)*
Medical doctor phone call/face-to-face interview			*(please see appendix 3 for cost calculation details)*
Screening scheduled	6.88		
Screening not scheduled	3.16		
Screening test	5.42		*(please see appendix 4 for cost calculation details)*
Workout of a positive screening test	171 [6]	137-171	
Treatment of a precancerous cervical lesion	696 [7]	557 - 696	Includes CIN 2 and CIN 3 lesions.
Treatment of an early stage cervical cancer	5229 [7]	4183 - 5229	This was computed assuming the mean cost between the treatment of a grade I and a grade II cervical cancer.
Treatment of a high stage cervical cancer	18326 [7]	14661 - 18326	This was computed assuming the mean cost between the treatment of a grade III and a grade IV cervical cancer.
End of life costs of patients with cervical cancer	64965 [8]	51972 - 64965	Comprises the costs of treatment, hospital stay, appointments and emergency room during the 6 months before death.
Description of health state	**Base case (QALY/year)†**	**Range**	**Further details**
Cervical cancer case that died	0		
Cervical cancer case that survives	0.715 [9]		The utility of 0.715 QALY/year was considered over a 5-year period. The utility was computed assuming that cervical cancer survivors have the lower stage of the tumor. Therefore, the mean utility of stage I and stage II was considered.
Women with precancerous lesion	0.9704 [10]		A utility of 0.9704 QALY was considered during a 1-year period. After the first year a utility of 1 was assumed.
Women with a positive screening test, but with no disease (false positive)	0.9967 [11]		The utility of a false positive test was considered. This was only assumed during a 1-year period. After this moment a utility of 1 was considered.

CIN - Cervical intraepithelial neoplasia. HPV - Human papillomavirus. QALY - Quality Adjusted Life Years. SMS - short message service text message. *All costs depicted were determined on a provider perspective. If a societal perspective is assumed, a total cost of 6.96€ will be added to all women who undergo screening. Details on cost calculation are presented in Appendixes 3 and 4. †Future benefits are discounted at a rate of 3% annually[24] ††The parameter to be varied in the sensitivity analysis is the proportion of successfully delivered automated SMS/phone calls/reminders (range: 0.68 to 0.85).

Table 2 - Costs, benefits, costs per unit of benefit and incremental cost effectiveness ratios, by strategy, on a provider and societal perspective.

Provider perspective

Strategy	% of women screened	Mean number of avoided deaths	Mean number of QALYs	Mean 5-year cost* (invitation + screening + treatment)	Cost/adherent women	Cost/death avoided	ICER†
(b)	43.0	0.999921	4.60773	22.74	-	-	-
(c)	50.6	0.999929	4.60783	23.19	5.92	50346	4286
(a)	34.0	0.999910	4.60761	23.85	SD	SD	SD
(d)	51.2	0.999930	4.60784	24.38	20.0	1964587	167230

Strategy	% of women screened	Mean invitation cost††	Cost/adherent women
(b)	43.0	0.09	-
(a)	34.0	0.80	SD
(c)	50.6	0.87	10.23
(d)	51.2	2.69	384.2

Societal perspective

Strategy	% of women screened	Mean number of avoided deaths	Mean number of QALYs	Mean 5-year cost* (invitation + screening + treatment)	Cost/adherent women	Cost/death avoided	ICER†
(b)	43.0	0.999921	4.60773	25.74	-	-	-
(a)	34.0	0.999910	4.60761	26.21	SD	SD	SD
(c)	50.6	0.999929	4.60783	26.71	12.76	110361	9394
(d)	51.2	0.999930	4.60784	27.94	26.83	2024603	172339

Strategy	% of women screened	Mean invitation cost††	Cost/adherent women
(b)	43.0	3.09	-
(a)	34.0	3.17	SD
(c)	50.6	4.39	17.19
(d)	51.2	6.24	354.7

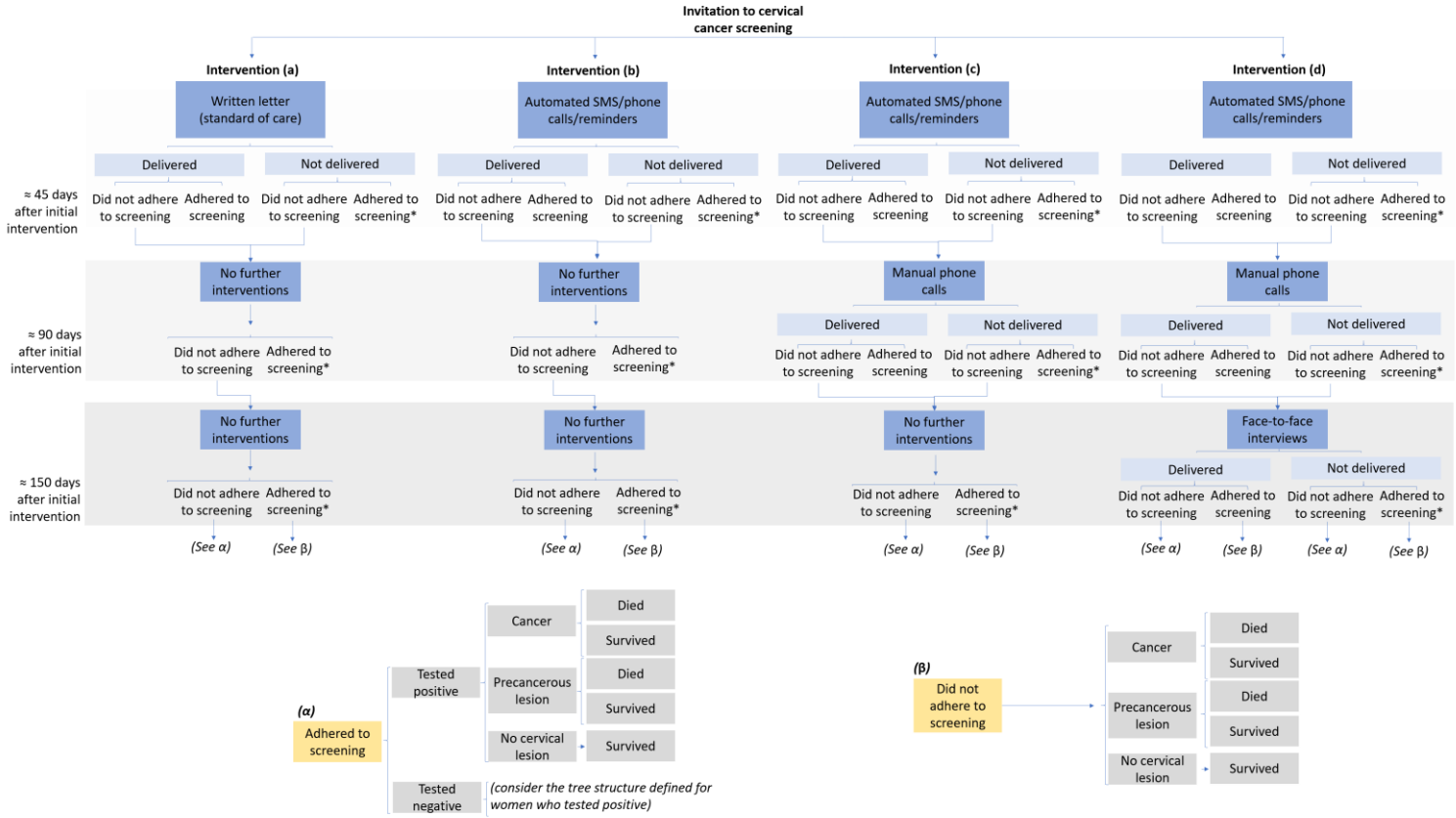
ICER - Incremental cost-effectiveness ratio. QALY - Quality Adjusted Life Years. SD - strongly dominated. SMS - short message service text message *Future costs and benefits were discounted at 3% annually, assuming a time-horizon of 5-years, based on the World Health Organization recommendations.[24] †Includes the costs of invitation, screening and treatment. ††The difference in cost divided by the difference in adherence of one strategy, compared with the next more effective strategy. ¶Includes only the invitation costs (i.e., does not comprise screening and treatment costs). §Strategy (a) - invitation based on a written letter, corresponding to the standard of care; Strategy (b) - invitation based on automated SMS/phone calls/reminders; Strategy (c) - invitation based on SMS/phone calls/reminders + manual phone calls; Strategy (d) - Invitation based on SMS/phone calls/reminders + manual phone calls + face-to-face interviews.

Table 3 - Sensitivity analysis.

Parameter to be varied in the sensitivity analysis		Parameter range*	Strategy†	ICER†† (provider perspective)	Strategy†	ICER†† (societal perspective)
Probability to successfully deliver automated SMS/phone calls	Min.	68%	(b)	-	(b)	-
			(c)	6565	(a)	SD
			(a)	SD	(c)	11675
			(d)	261369	(d)	266478
	Max	85%	(b)	-	(b)	-
			(c)	4205	(a)	SD
			(a)	SD	(c)	9314
			(d)	165636	(d)	170744
Workout costs of a positive screening test	Min.	137 €	(b)	-	(b)	-
			(c)	3876	(a)	SD
			(a)	SD	(c)	8985
			(d)	166820	(d)	171929
	Max	171 €	(b)	-	(b)	-
			(c)	4279	(a)	SD
			(a)	SD	(c)	9387
			(d)	167223	(d)	172332
Treatment costs of a precancerous lesion	Min.	557 €	(b)	-	(b)	-
			(c)	5203	(a)	SD
			(a)	SD	(c)	10312
			(d)	168148	(d)	173256
	Max	696 €	(b)	-	(b)	-
			(c)	3784	(a)	SD
			(a)	SD	(c)	8893
			(d)	166729	(d)	171837
Treatment costs of an early stage lesion	Min.	4 183 €	(b)	-	(b)	-
			(c)	4442	(a)	SD
			(a)	SD	(c)	9551
			(d)	167387	(d)	172496
	Max	5 229 €	(b)	-	(b)	-
			(c)	4199	(a)	SD
			(a)	SD	(c)	9308
			(d)	167144	(d)	172252
Treatment costs of a high stage lesion	Min.	14 661 €	(b)	-	(b)	-
			(c)	4486	(a)	SD
			(a)	SD	(c)	9595
			(d)	167431	(d)	172539
	Max	18 326 €	(b)	-	(b)	-
			(c)	4174	(a)	SD
			(a)	SD	(c)	9283
			(d)	167119	(d)	172228
End-of-life costs	Min.	51 972 €	(b)	-	(b)	-
			(c)	5077	(a)	SD
			(a)	SD	(c)	10185
			(d)	168021	(d)	173130
	Max	64 965 €	(b)	-	(b)	-
			(c)	3971	(a)	SD
			(a)	SD	(c)	9079
			(d)	166915	(d)	172024
5-year relative survival among women with a confirmed cervical cancer, who previously tested positive on the screening test	Min.	0.804	(b)	-	(b)	-
			(c)	4622	(a)	SD
			(a)	SD	(c)	9796
			(d)	169630	(d)	174804
	Max.	0.982	(b)	-	(b)	-
			(c)	3957	(a)	SD
			(a)	SD	(c)	9003
			(d)	164890	(d)	169935
5-year relative survival among women with a confirmed cervical cancer, who previously tested negative on the screening test	Min.	0.716	(b)	-	(b)	-
			(c)	4464	(a)	SD
			(a)	SD	(c)	9608
			(d)	168506	(d)	173649
	Max.	0.875	(b)	-	(b)	-
			(c)	4106	(a)	SD
			(a)	SD	(c)	9181
			(d)	165956	(d)	171030
5-year relative survival among women with a confirmed cervical cancer, who were not adherent to organized cervical cancer screening	Min.	0.679	(b)	-	(b)	-
			(c)	1972	(a)	SD
			(a)	SD	(c)	6636
			(d)	150726	(d)	155390
	Max.	0.829	(b)	-	(b)	-
			(c)	7087	(a)	SD
			(a)	SD	(c)	12735
			(d)	187215	(d)	192863
Correction applied to the adherence determined after strategy (b), to consider the expected increase over time due to opportunistic invitations¶	Min.	0%	(b)	-	(b)	-
			(c)	1694	(a)	SD
			(a)	SD	(c)	6802
			(d)	167230	(d)	172339
	Max.	8.3%	(b)	-	(b)	-
			(c)	14104	(a)	SD
			(a)	SD	(c)	19213
			(d)	167230	(d)	172339
Correction applied to the adherence determined after strategy (c), to consider the expected increase over time due to opportunistic invitations¶	Min.	0%	(b)	-	(b)	-
			(c)	6974	(a)	SD
			(a)	SD	(c)	12082
			(d)	31044	(d)	37152
	Max.	3.3%	(b)	-	(b)	-
			(c)	3187	(a)	SD
			(a)	SD	(c)	8296
			(d)	SD	(d)	SD

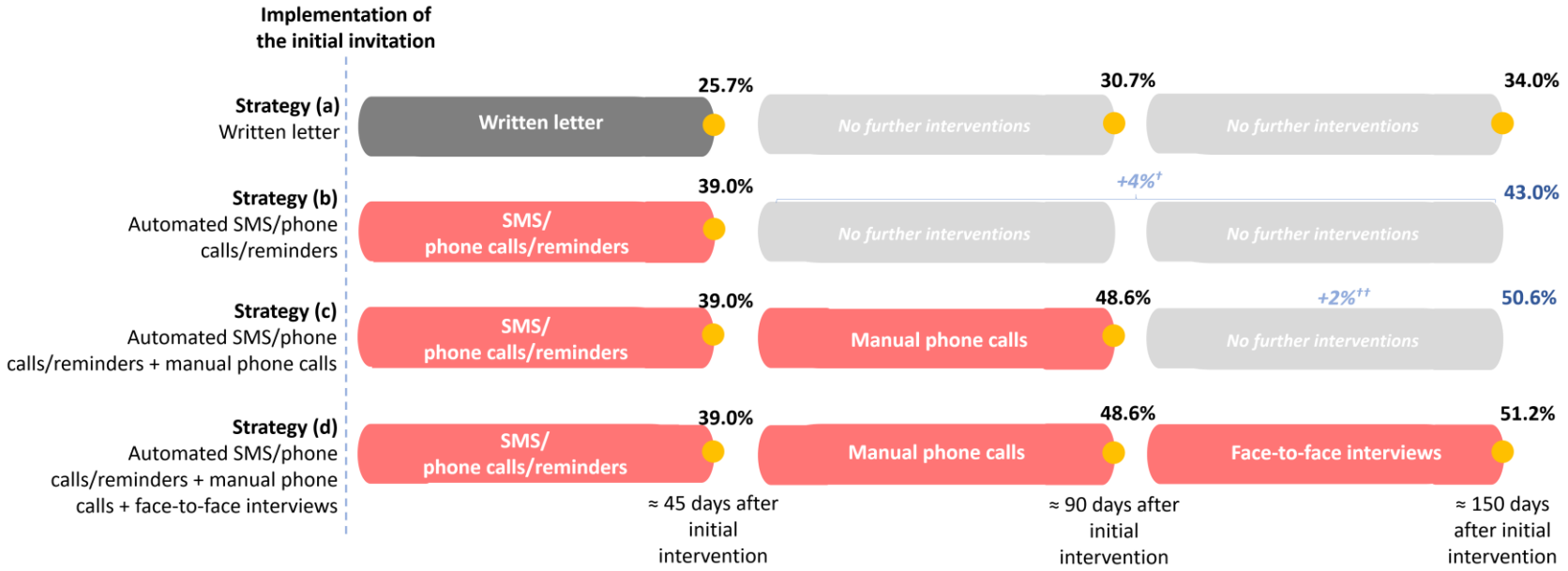
ICER - incremental cost-effectiveness ratio. SD - strongly dominated. SMS - short message service text message. *The table depicts the minimum and maximum value of the parameters assumed in the sensitivity analysis and the corresponding ICERs. †Strategy (a) - written letter; Strategy (b) - SMS/phone calls/reminders; Strategy (c) - automated SMS/phone calls/reminders + manual phone calls; Strategy (d) - SMS/phone calls/reminders + manual phone calls + face-to-face interviews. ††The difference in cost divided by the difference in adherence of one strategy, compared with the next more effective strategy. All the ICER values were computed using a cost-effectiveness model that assumes as outcome the number of Quality Adjusted Life Years. ¶Since the adherence after strategy (b) and (c) was not determined 150 days after implementing these interventions (as conducted for strategies (a) and (d)), a correction factor was applied to consider the possible effect of opportunistic invitations (Appendix 1). The minimum value of zero corresponds to the unlikely scenario where no opportunistic invitations occur. The values of 8.3% and 3.3% correspond to the opportunistic adherence values observed in the control group of SCAN trial that were assumed as the highest estimates possible to occur (Appendix 1).

Figure 1 – Decision tree model overview.



SMS - short message service text messages. *Women not receiving the tested intervention may undergo screening after an invitation made by their family doctors, during appointments scheduled for other health reasons

Appendix 1 – Description of the competing interventions tested in the SCAN-Cervical Cancer Trial*



SCAN – Stepwise strategy to improve cervical cancer screening adherence. SMS – short message service text message.

*The standard of care strategy of women invitation to cervical cancer screening is depicted in dark grey. The strategies represented in pink were tested as interventions in SCAN-Cervical Cancer trial. Orange circles represent the timepoints considered for the outcome assessment in the SCAN-Cervical Cancer trial. Bold figures represent the observed adherence proportions to cervical cancer screening. For interventions (b) and (c) the adherence to cervical cancer screening was determined on SCAN-Cervical Cancer trial 45 and 90 days after the initial invitation, respectively. Therefore, to ensure an accurate comparison between strategies (a), (b), (c) and (d), the adherence to cervical cancer screening should have been determined in the same timepoint (i.e., 150 days after the initial invitation). However, the SCAN-Cervical Cancer trial only assessed the outcome at this timepoint for strategy (a) and (d). For the remaining strategies, we expect that women may be opportunistically invited by their family doctors to screening during appointments scheduled for other health purposes, increasing the adherence to screening. To consider the possible effect of opportunistic invitations after strategies (b) and (c), an expected increase in adherence of 4% and 2% was applied, respectively; the corrected adherence estimates after strategy (b) and (c) are depicted in dark blue. †This parameter was varied in the sensitivity analysis between 0 and 8.8% (please see Table 3 for further details). ††This parameter was varied in the sensitivity analysis between 0 and 3.3% (please see Table 3 for further details)

Appendix 2 - Detailed description of the transition probabilities for each invitation strategy*

Written letter (strategy a)	**p**
Probability of delivery of the written letter	0.990
Probability of adherence to cervical cancer screening 45 days after a delivered written letter	0.259
Probability of adherence to cervical cancer screening 90 days after a delivered written letter, among previously non-adherent women	0.067
Probability of adherence to cervical cancer screening 150 days after a delivered written letter, among previously non-adherent women	0.048
Probability of adherence to cervical cancer screening 45 days after a non-delivered written letter	0
Probability of adherence to cervical cancer screening 90 days after a non-delivered written letter, among previously non-adherent women	0.167
Probability of adherence to cervical cancer screening 150 days after a non-delivered written letter, among previously non-adherent women	0
Automated SMS/phone calls/reminders (strategy b)	**p**
Probability of delivery of automated SMS/phone calls/reminders	0.843
Probability of adherence to cervical cancer screening 45 days after delivered SMS/phone calls/reminders	0.435
Probability of adherence to cervical cancer screening 45 days after non-delivered SMS/phone calls/reminders	0.147
Probability of adherence to cervical cancer screening 150 days after the initial invitation, among women who did not adhere to screening 45 days after SMS/phone calls/reminders	0.066
Manual phone calls (strategy c)	**p**
Probability of scheduling a screening appointment after a manual phone call, among women to whom automated SMS/phone calls/reminders were delivered	0.361
Probability of scheduling a screening appointment after a manual phone call, among women to whom automated SMS/phone calls/reminders were not delivered	0.160
Probability of adherence to cervical cancer screening among women who scheduled a screening appointment, after receiving automated SMS/phone calls/reminders	0.471
Probability of adherence to cervical cancer screening among women who scheduled a screening appointment, after not receiving automated SMS/phone calls/reminders	0.231
Probability of adherence to cervical cancer screening among women who did not schedule a screening appointment, after receiving automated SMS/phone calls/reminders	0.033
Probability of adherence to cervical cancer screening among women who did not schedule a screening appointment, after not receiving automated SMS/phone calls/reminders	0
Expected probability of adherence to cervical cancer screening 150 days after the initial invitation, among women who did not adhere to screening 45 days after a manual phone call	0.039
Face-to-face interviews (strategy d)	**p**
Probability of scheduling a screening appointment after a face-to-face interview, among women to whom automated SMS/phone calls/reminders were delivered and a screening appointment was scheduled after a manual phone call	0.290
Probability of scheduling a screening appointment after a face-to-face interview, among women to whom automated SMS/phone calls/reminders were delivered and a screening appointment was not scheduled after a manual phone call	0.067
Probability of scheduling a screening appointment after a face-to-face interview, among women to whom automated SMS/phone calls/reminders were not delivered and a screening appointment was scheduled after a manual phone call	0.300
Probability of scheduling a screening appointment after a face-to-face interview, among women to whom automated SMS/phone calls/reminders were not delivered and a screening appointment was not scheduled after a manual phone call	0
Probability of adherence to cervical cancer screening among women who scheduled a screening appointment during a face-to-face interview, after receiving SMS/phone calls/reminders and scheduling a screening appointment during a manual phone call	0.188
Probability of adherence to cervical cancer screening among women who did not schedule a screening appointment during a face-to-face interview, after receiving SMS/phone calls/reminders and scheduling a screening appointment during a manual phone call	0.032
Probability of adherence to cervical cancer screening among women who scheduled a screening appointment during a face-to-face interview, after receiving SMS/phone calls/reminders and not scheduling a screening appointment during a manual phone call	0.417
Probability of adherence to cervical cancer screening among women who did not schedule a screening appointment during a face-to-face interview, after receiving SMS/phone calls/reminders and not scheduling a screening appointment during a manual phone call	0.024
Probability of adherence to cervical cancer screening among women who scheduled a screening appointment during a face-to-face interview, after not receiving SMS/phone calls/reminders and scheduling a screening appointment during a manual phone call	0.667
Probability of adherence to cervical cancer screening among women who did not schedule a screening appointment during a face-to-face interview, after not receiving SMS/phone calls/reminders and scheduling a screening appointment during a manual phone call	0
Probability of adherence to cervical cancer screening among women who scheduled a screening appointment during a face-to-face interview, after not receiving SMS/phone calls/reminders and not scheduling a screening appointment during a manual phone call	0
Probability of adherence to cervical cancer screening among women who did not schedule a screening appointment during a face-to-face interview, after not receiving SMS/phone calls/reminders and not scheduling a screening appointment during a manual phone call	0.015

SMS - short message service text message. *All probabilities presented were obtained from the Stepwise strategy to improve cervical cancer screening adherence (SCAN-Cervical Cancer trial).

Appendix 3 - Cost calculation details for the competing interventions.

	Cost (€) per month	Cost (€) per unit	Auxiliary information for calculation
Provider perspective			
Invitation letter		**0.8**	
Paper, envelope and post-office service		0.4	
Human resources - printing*	1300†	8.125	Written letters were manually printed and enveloped as usually performed. A secretary was able to print and envelope an invitation letter in 3 minutes.
Automated SMS/phone calls and reminders			
Invitation delivered		**0.1**	
Invitation SMS	19.9††	0.004	A total of 5000 text messages or 5000 minutes of phone calls were performed with a cost per month of 19.9€.
Automated phone call	19.9††	0.004	This cost was only considered for those women who picked up the phone call (≈31%).
Reminder SMS	19.9††	0.004	The reminder SMS was only sent to women who confirmed the appointment, corresponding to 41.7% of them.
Software to customize and send the SMS and automated phone calls	77.76††	0.001	The software costs were diluted by the total number of women eligible for cervical cancer screening each year in Portugal.
Human resources (primary care unit secretaries) to train the users of the software*	1300†	8.125	A primary care unit secretary was able to train 5 trainees in 1h. Each trainee was able to perform all the eligible women in one primary care unit secretary (≈1000 women). The training was considered valid for 5 years.
Human resources (primary care unit secretaries) training on how to use the software*	1300†	8.125	A primary care unit secretary was trained in 1h. Each trainee was able to invite all the eligible women in one primary care unit secretary (≈1000 women). The training was considered valid for 5 years.
Human resources (primary care unit secretaries) to send the SMS/automated phone calls/reminders*	1300†	8.125	A primary care unit secretary was able to send a batch of 200 women in 1h.
Human resources (primary care unit secretaries) for appointment reschedule, whenever asked by the participant*	1300†	8.125	Only 8.9% of the invited women asked to reschedule the appointment. To reschedule, the primary care unit secretary used 4.2 min/women (0.07 hours).
Phone call - rescheduling	19.9††	0.004	Only 8.9% of the invited women asked to reschedule the appointment. The primary care unit secretary used 4.2 min/women.
Invitation not delivered (SMS/phone calls/reminders were not delivered)		**0.05**	
Invitation SMS	19.9††	0.004	All the women did not receive the invitation text message, so a second invitation was sent.
Software to customize and send the SMS/phone calls/reminders	77.76††	0.001	(see above)
Human resources (primary care unit secretaries) to train the users of the software*	1300†	8.125	(see above)
Human resources (primary care unit secretaries) training on how to use the software*	1300†	8.125	(see above)
Human resources (primary care unit secretaries) to send the SMS/phone calls/reminders*	1300†	8.125	(see above)
Manual phone call		**1.273**	
Phone call	19.9††	0.004	The mean phone call duration was 2 minutes/women invited (0.03h). Only 44.8% of the women picked-up the phone call.
Human resources (primary care unit secretaries) to perform the manual invitation phone call*	1300†	8.125	The mean duration of the invitation was 9.3 minutes/women invited (0.155h).
Human resources (primary care unit secretaries) to train the secretaries who will perform the invitation phone calls*	1300†	8.125	A primary care unit secretary trained 5 trainees in 1h. Each trainee was able to interview all the eligible women registered in each medical doctor patient list (≈200 women). The training was considered valid for 5 years.
Human resources (primary care unit secretaries) training on how to perform an invitation phone call*	1300†	8.125	A primary care unit secretary was trained in 1h. Each trainee was able to interview all the eligible women registered in one medical doctor patient list (≈200 women). The training was considered valid for 5 years.

(continuation of Appendix 3)

	Cost(€) per month	Cost (€) per unit	Auxiliary information for calculation
Provider perspective			
Face-to-face interviews			
Screening scheduled		**6.877**	
Phone call	19.9[††]	0.004	Only 19.3% of the invited women picked-up the invitation phone call.
Human resources (medical doctor resident) to perform the manual invitation phone calls[*]	1800[¶]	11.25	The medical doctor used a mean of 16.7 (0.28h) minutes to perform the invitation phone call. A regular wage salary was considered.
Human resources (medical doctor resident) to perform the face-to-face interview[*]	1800[¶]	11.25	The medical doctor used a 20-minute (0.33h) appointment, which is the standard appointment duration.
Human resources (primary care unit secretaries) to perform the check-in of women who attend the face-to-face interview[*]	1300[†]	8.125	A 5-minute (0.08h) check-in time was considered.
Human resources (medical doctor resident) to train the interviewers[*]	1800[¶]	11.25	A medical doctor resident was able to train 5 trainees in 1h.
Human resources (medical doctor resident) training to perform the interviews[*]	1800[¶]	11.25	A medical doctor resident was trained in 1h. Each trainee was able to interview all the eligible women registered in his patient list (≈200 women). The training was considered valid for 5 years.
Screening not scheduled		**3.164**	
Phone call	19.9[††]	0.004	(see above)
Human resources (medical doctor resident) to perform the manual invitation phone call[*]	1800[¶]	11.25	(see above)
Human resources (medical doctor resident) to train the interviewers[*]	1800[¶]	11.25	(see above)
Human resources (medical doctor resident) training to perform the interviews[*]	1800[¶]	11.25	(see above)
Societal perspective[§]			
Opportunity costs of participants	557	3.481	(see footnote)
Travel costs of participants	557	3.481	(see footnote)

SMS - short message service text messages. *Health care professionals' time consumption per procedure was determined by direct observation of health professionals of two (randomly selected) primary care units. An average time was calculated by taking the mean time of five of the same procedures performed by three different health professionals in both primary care units. We used Portuguese Health Ministry public sources to derive salary costs.[1,2] †A wage of 1300€/month was considered, based on the regular salary of a clinical secretary salary and a 25% increase to consider the production incentives usually applied in Portuguese Primary Care Units.[1] ††Unit costs of the invitation method and software were obtained from a standard private provider. ¶A wage of 1800€/month was considered based on the publicly available data from the Portuguese health costs center (Administração Central dos Serviços de Saúde).[2] §Costs due to work time lost were determined by multiplying the number of hours lost due to treatments by the Portuguese minimum wage salary (557€ per month), which corresponds to 3.48€ per hour.[3] Opportunity costs were fixed at 6.96€ per visit (with an estimated two hours of time spent per visit) and travel costs at 3.48€.

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Appendix 4 - Cost calculation details for cervical cancer screening, treatment and end of life care. *

	Cost per month (€)	Cost per unit (€)	Auxiliary information for calculations
Costs of screening, treatment and end of life care			
Screening			
Human resources (medical doctor specialist)	3158.2	18.2	The medical doctor used a 20-minute (0.33h) appointment, which is the standard appointment time for screening.
Cytology kit		0.97†	
Laboratory tests		5.42††	
Workout of a positive screening test		171.6[1]	This estimate was corrected for inflation and purchasing power.
Treatment of a precancerous cervical lesion		696.5[2]	Includes CIN 2 and CIN 3 lesions. The available estimate was corrected for inflation and purchasing power.
Treatment of an early stage cervical cancer		5229.0[2]	This was computed assuming the mean cost between the treatment of a stage I and a stage II cervical cancer. The available estimate was corrected for inflation and purchasing power.
Treatment of an advanced stage cervical cancer		18326.0[2]	This was computed assuming the mean cost between the treatment of a stage III and a stage IV cervical cancer. The available estimate was corrected for inflation and purchasing power.
End of life care costs of patients with cervical cancer		64965.1[3]	This estimate comprises the costs of treatment, hospital stay, appointments, emergency room during the six months before death. This parameter was corrected for inflation and purchasing power.

CIN - Cervical intraepithelial neoplasia. *The costs of screening, workout of a positive screening test, treatment of a cervical cancer screening and end-of-life care costs of a patient with cervical cancer screening were obtained from the National Accounting Institution for Health in Portugal (ACSS) or if not available, estimated according to the international available literature. †This information was not publicly available in Portugal, so we considered the cost estimates from Medicaid.[4] ††This information was based on the regular price defined by the Portuguese government.[5]

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4 | GENERAL DISCUSSION AND CONCLUSIONS

This thesis used a methodologically robust randomized controlled trial to show that a stepwise strategy of invitation to cervical cancer screening, based on automated text messages/phone calls/reminders (step 1), manual phone calls (step 2) and face-to-face interviews (step 3), as well as invitation strategies based on step 1 or steps 1+2, were significantly more effective than the standard of care (Papers I, II, IV).

The implementation of the proposed invitation strategies at a population level requires solid evidence regarding their effectiveness, but also on their cost-effectiveness, which was analyzed in Paper V. This study showed that an invitation to cervical cancer screening based on steps 1+2 was very cost-effective, both from the societal and provider perspectives, surpassing the standard of care, as well as the interventions based on step 1 or steps 1+2+3, when the willingness-to-pay threshold is defined at one time the Portuguese gross domestic product per capita.

This thesis adds to previous research on strategies to increase adherence to cervical cancer screening an essentially pragmatic and population-based assessment of a stepwise intervention, with a clear gradient of customization and cost, combining easy-to-implement strategies with highly customized interventions. This was also one of the few investigations supporting the implementation of a new invitation strategy for organized cervical cancer screening with a detailed cost-effectiveness analysis that considers high quality patient-level data. The major limitations of the previously published articles on this topic[91,94,95,97,103,106], were surpassed by our study that considered QALYs as the outcome of the cost-effectiveness models and not only adherence to cervical cancer screening, but also through the quantification of costs and benefits both from the provider and societal perspective.

Some overall limitations should be addressed regarding the studies conducted. Although women aged 25 to 65 years are considered eligible for cervical cancer screening, the SCAN trial only included those below 50 years of age, who use their mobile phones more often and benefit the most from the proposed interventions.[108] Therefore, the conclusions of this thesis may not apply to older women, who may have different digital skills, despite most of Portuguese women, aged 50 years or above, already use their mobile phone on a daily basis.[108] Additionally, the proposed multistep intervention considered automated strategies, but also manual phone calls and face-to-face interviews which are expected to be easily accepted by women with less digital literacy. Women with no available mobile phone registered in the National Health Service database were considered not eligible, since the tested interventions require a functional mobile phone number to be delivered. However, since less than 3% of the potentially eligible women were

excluded before randomization due to this criterion, this is expected to have a limited impact on the conclusions drawn in Papers II and IV. Regarding women randomized to the intervention group, a large proportion had an invalid mobile phone number, precluding the delivery of the tested strategies, reducing their effectiveness. However, due to the ongoing improvement of mobile phone number records in Portugal, the effect of the tested interventions is expected to increase, potentially reaching the values calculated in the per-protocol analyses.[109]

Approximately 50% of the invited primary health care units refused to participate in the current trial and among those who were enrolled in the study, around 20% did not apply step 3 intervention. This may be explained because the medical doctors of the primary health care units have limited time available in their clinical schedule to implement the face-to-face interviews (step 3 intervention). However, this is not expected to limit the regular use of an intervention based on steps 1+2 (*i.e.*, the most cost-effective invitation strategy), since it is based on automated text messages/phone calls/reminders and manual phone calls, that do not require the direct participation of medical doctors to be implemented. Additionally, if step 1+2 intervention is defined as the standard of care invitation to cervical cancer screening, it is anticipated that the Ministry of Health will define time periods in the clinical secretaries' schedules just to perform manual phone calls, contributing for a higher adoption of this strategy. Considering the previous arguments, a higher adoption of step 1+2 intervention is expected to occur if it is implemented at a national level, increasing the effectiveness of this strategy and contributing to reduce the difference between the computed intention-to-treat and per-protocol effect estimates. Contamination may have occurred, because women can undergo screening for free and the participants randomized to the intervention group may live geographically near to those in the control group. However, if contamination has occurred, it would reduce the difference between groups, resulting in conservative effect estimates.

The conducted cost-effectiveness analysis considered a 5-year time-frame, which has the advantage of using reliable parameters, namely survival estimates, that are usually calculated five years after the diagnosis of a cervical cancer or a pre-malignant disease. A life-time perspective could have been used instead, including longer-term benefits, that are expected to occur due to a carryover effect of the intervention, resulting in lower cost-effectiveness ratios. However, this approach would require the use of life-time costs and survival parameters in the decision tree model, which are often imprecise and difficult to estimate. Additionally, a sensitivity analysis showed that the invitation based on steps 1+2 is expected to remain the most cost-effective strategy, even if the number of QALYs of all the tested interventions increases 10% (analysis not presented in Paper V).

The evidence produced with this thesis was disseminated through academic publications and presentations in scientific conferences. Study findings were also communicated to the involved primary health care units and professionals through face-to-face meetings, with the support of customized reports, which were assembled using the two-page template proposed in Paper III. The conclusions of this work were presented to the coordinators of the organized screening programs of the North and Lisbon Health Regions of Portugal (*Administração Regional de Saúde do Norte* and *Administração Regional de Saúde de Lisboa e Vale do Tejo*). All these communication strategies were used to promote the adoption of automated text messages/phone calls/reminders and manual phone calls as the new invitation method for cervical cancer screening, since this strategy is more effective and cost-effective than the standard of care.

In conclusion, the results of this thesis support the implementation of automated text messages/phone calls/reminders and manual phone calls as the new standard of care invitation to cervical cancer screening, under a willingness-to-pay threshold of one time the Portuguese gross domestic product per capita. The implementation of this strategy may be expected to increase the cost-effectiveness of organized screening and have a positive impact on the population's health.

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