Gynecologic Oncology 168 (2023) 39–47

Contents lists available at ScienceDirect

Gynecologic Oncology

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

The cost-effectiveness of opt-in and send-to-all HPV self-sampling among long-term non-attenders to cervical cancer screening in Norway: The Equalscreen randomized controlled trial

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HIGHLIGHTS

- Self-sampling long-term under- and non-screeners increases costs but detects more high-grade precancers than reminder letters.
- In the Norwegian context, self-sampling is likely to be considered high-value and cost-effective.
- The preferred HPV-ss delivery depends on a decision maker's willingness-to-pay for these health benefits.

ARTICLE INFO

Article history:
Received 8 August 2022
Received in revised form 12 October 2022
Accepted 31 October 2022
Available online 11 November 2022

Keywords:
Human papillomavirus
Cervical cancer
Self-sampling
Cost-effectiveness

ABSTRACT

Objective. We assessed the cost-effectiveness of mailing a human papillomavirus self-sampling (HPV-ss) kit, directly or via invitation to order, compared with mailing reminder letters among long-term non-attenders in Norway.

Methods. We conducted a secondary analysis using the Equalscreen study data with 6000 women aged 35–69 years who had not screened in 10+ years. Participants were equally randomized into three arms: reminder letter (control); invitation to order HPV-ss kit (opt-in); directly mailed HPV-ss kit (send-to-all). Cost-effectiveness (2020 Great British Pounds (GBP)) was estimated using incremental cost-effectiveness ratios (ICERs) per additional screened woman, and per additional cervical intraepithelial neoplasia grade 2 or worse (CIN2+) from extended and direct healthcare perspectives.

Results. Participation, CIN2+ detection, and total screening costs were highest in the send-to-all arm, followed by the opt-in and control arms. Non-histological physician appointments contributed to 67% of the total costs in the control arm and ≤ 31% in the self-sampling arms. From an expanded healthcare perspective, the ICERs were 135 GBP and 169 GBP per additional screened woman, and 2864 GBP and 4165 GBP per additional CIN2+ detected for the opt-in and send-to-all, respectively.

Conclusions. Opt-in and send-to-all self-sampling were more effective and, depending on willingness-to-pay, may be considered cost-effective alternatives to improve screening attendance in Norway.

1. Introduction

Organized screening programs with a high population coverage have contributed to a decline in cervical cancer incidence and mortality [1,2]. Despite a well-established, reminder letter-based program, 320 women were diagnosed and 106 women died from cervical cancer in Norway in 2020 [3]. National screening coverage in Norway has

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https://doi.org/10.1016/j.ygyno.2022.10.027

stagnated at approximately 80% within a 5.5 year period [4]. Among women aged 35–69 years eligible for screening in Norway, approximately 17% have not screened in ten or more years [4]. Under- and non-screened women have both a higher risk of developing cervical cancer [5] and of being diagnosed at a more progressed cancer stage [6,7] compared to women routinely screened at recommended intervals. Finding new methods to engage this hard-to-reach segment of the population could be instrumental in improving Norway's screening coverage.

HPV self-sampling (HPV-ss) allows for self-collection, removing the potential barrier of a clinical appointment. HPV-ss has been found to have a high level of acceptability [8] and similar accuracy as physician-collected samples [9]. HPV-ss may be programmatically delivered to women via two approaches. The send-to-all method, where women are directly mailed an unsolicited self-sampling kit, has proven to increase screening participation in under-screeners in Norway [10] and a recent meta-analysis of studies from several countries confirmed this finding [9]. Alternatively, opt-in methods, where women order a self-sampling kit, have had mixed results where one trial reported increased participation [11], and a meta-analysis reported opt-in self-sampling to not be any more effective than standard reminder letters [12]. However, few studies have evaluated alternative HPV-ss delivery methods on women who have not screened in 10 or more years [7,13,14].

The Equalscreen trial was designed to examine opt-in vs send-to-all screening strategies and their effect on screening participation among women who have not screened for cervical cancer in 10 or more years. The trial concluded that self-sampling increased screening participation among long-term under- and non-screeners, as the opt-in and send-to-all arms yielded 3.5 to nearly 6 times greater participation rates, respectively, when compared to the control arm (standard reminder letters) [7]. Prior to implementation, Norwegian policymakers require that health economic consequences of new interventions are quantified, enabling more informed decisions that weigh both the costs and benefits of the strategies [15]. Although previous CEAs have been performed to examine the value of HPV-ss [16–18], to our knowledge, no CEAs have evaluated opt-in versus send-to-all delivery approaches among long-term under- and non-screeners. The objective of this study was to evaluate the cost-effectiveness of HPV-ss, either as an offer to order a self-sampling kit (opt-in) or a directly mailed self-sampling kit (send-to-all), with standard reminder letters (control) for long-term under- and non-screeners in Norway.

2. Materials and methods

This CEA is a secondary analysis based on clinical data from the Equalscreen randomized trial, the methods of the trial have been described previously [7], and the original report of this clinical trial conformed to the CONSORT 2010 statement [19].

2.1. Study design

As previously described [7], the Equalscreen trial included women aged 35–69 years who had not screened in 10+ years residing in four counties in Norway. Using the CervicalScreen database, 28,125 eligible women were identified, of which 6000 were randomly invited to participate in the study. The women were randomized at a 1:1:1 ratio into three intervention arms: i) control, ii) opt-in, and iii) send-to-all. The study flowchart is shown in Fig. 1.

2.2. Interventions

2.2.1. Control arm

In the "control" arm, women were sent a standard reminder letter to attend screening (i.e., to schedule an appointment with their GP)

2.2.2. Opt-in arm

In the "opt-in" arm, women were mailed an invitation letter to order a self-sampling kit. Each invitation came with a unique order code, a reply slip, and a pre-paid envelope to return the self-sample. Only one HPV-ss kit could be ordered per order code. Women who had not returned a valid self-sample within 3 weeks of invitation were sent one reminder letter

2.2.3. Send-to-all arm

In the "send-to-all" arm, women were directly mailed a self-sampling kit. The invitation and self-sampling instructions were the same as provided to the opt-in arm except for the information on ordering a kit.

2.3. Screening procedures

2.3.1. In-office screeners

Women in the control arm or one of the HPV-ss arms who opted to attend a GP or gynaecologist (instead of using the HPV-ss option) for screening within six months of invitation were classified as "in-office screeners". Samples taken by a physician were analyzed via cytology or hrHPV test. Any non-normal (i.e., atypical cells of unknown significance (ASC-US) or worse, or hrHPV-positive) results prompted a reflex test performed on the original sample. Women were responsible to pay a deductible for in-office appointments. In-office screening was managed per national guidelines [20].

2.3.2. Self-sampling screeners

Women who returned a valid HPV self-sample within six months of invitation were classified as self-sampling screeners. Details on sampling material, processing of samples, and HPV analysis are described in the Equalscreen trial guidelines [7]. Self-sampling kits were provided free-of-charge. Women who returned a self-sample were informed of their result via ordinary mail within six weeks after their sample was received by the laboratory. Women who had a negative hrHPV-ss result were encouraged to follow regular screening at the recommended interval. Women who had a positive hrHPV-ss result were provided with a pre-scheduled 'triage' appointment to have cytology performed by a physician. Triage appointments were sequentially allocated to either their GP or a selected gynaecologist. Triage GPs were instructed to take a cytology sample, whereas gynecologists were to take a cytology sample as well as perform colposcopy and biopsy, if necessary. Women who did not have a cytology test registered within three months following the scheduled appointment were sent a reminder letter encouraging them to schedule an appointment with their GP. A woman was considered to have participated in triage if an appointment was attended, whether at the trial-allocated physician or not, within six months of notification of a positive hrHPV-ss. The physicians were informed the woman had tested positive for hrHPV via self-sampling as part of a study. Women were responsible for paying the deductible for triage appointments. Any further management after the scheduled triage appointment was to follow national guidelines, as noted above [20]. Women who attended triage outside their scheduled appointment were managed outside of the study (but recorded in the national screening registry) and were to follow national guidelines.

2.4. Registry data collection

The last linkage to registry data (screening, histology and cancer registries) was December 2020, which provided a minimum of 16 months of follow-up after the invitation to the study. See Equalscreen trial [7] for additional details on registry data collection.

2.5. Cost-effectiveness analysis

For this CEA, the primary and secondary outcomes of the Equalscreen trial (participation and detection of CIN2+, respectively)

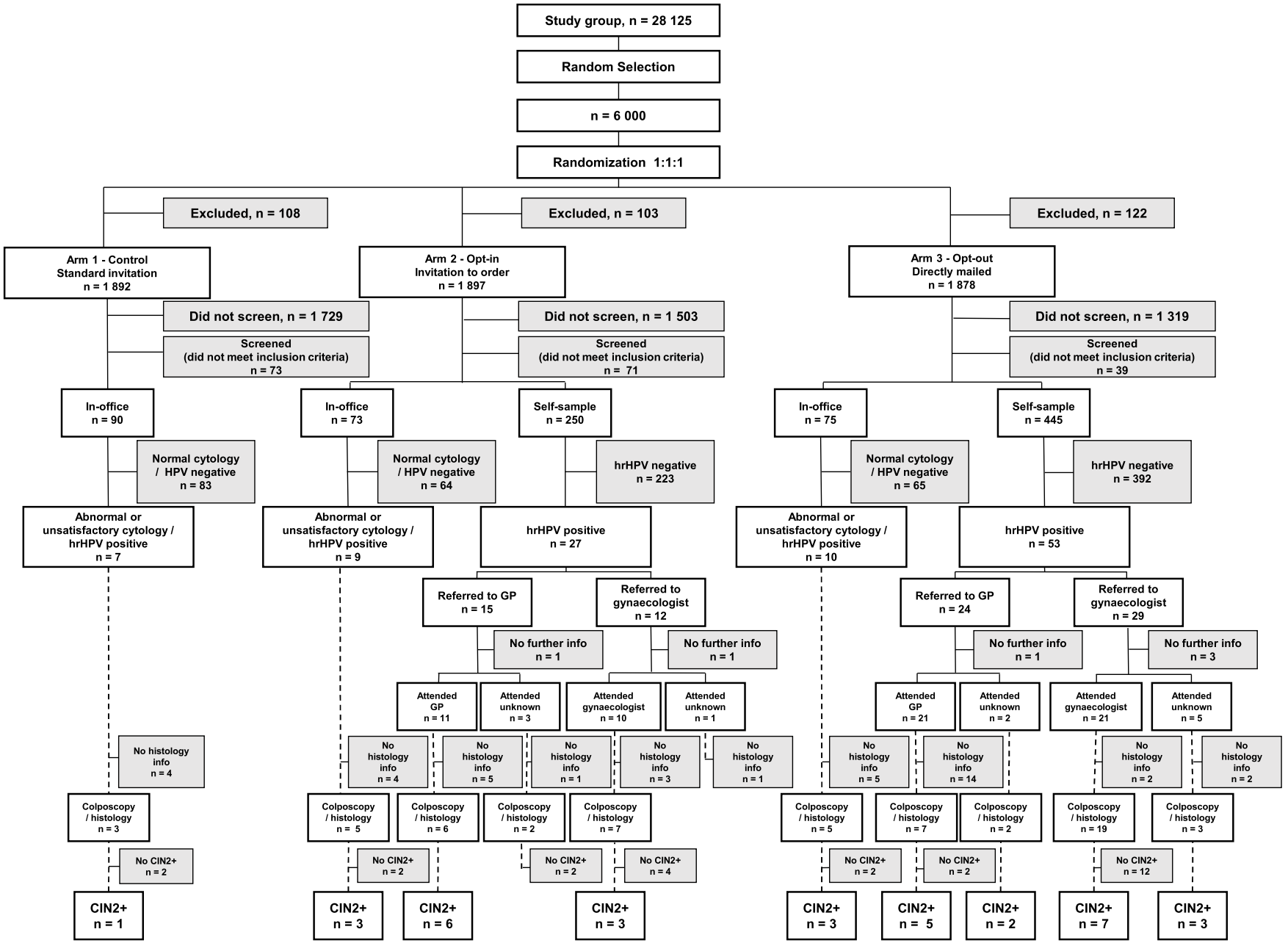

Fig. 1. Equalscreen study flowchart with number of women at different stages of the trial. Each woman in the three trial arms was followed until the detection of cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+) or end of observation period. Solid lines represent direct movement from one screening stage to another, while the dotted lines represent the possibility of more than one appointment as some women had more than one physician-based appointment before attending a colposcopy/histology appointment or before the detection of CIN2+. One woman (send-to-all arm, self-sampling hrHPV positive, referred to gynaecologist) attended triage after the six-month inclusion window and was not included as "attended unknown" in the flowchart. The woman was not detected with CIN2+. Costs were converted from 2020 Norwegian kroner (NOK) to 2020 British pounds (GBP, 1 NOK = 0.0829 GBP [23]. Abbreviations: HPV = human papillomavirus, GP = general practitioner.

were used as health measures to evaluate the short-term effectiveness and economic costs associated with the three alternative approaches. As recommended by Norwegian guidelines [21], we conducted our RCT-based CEA from an extended healthcare perspective but also considered a narrower, direct healthcare perspective in scenario analysis. The direct healthcare perspective included the direct unit costs associated with screening and treatment procedures (i.e., laboratory analysis, personnel, materials, postage), while the extended healthcare costs included the direct costs as well as the women's time and travel costs associated with each screening-related event. We used the length of the trial as our time horizon (March 2019 – December 2020), i.e., a minimum of 16 months follow-up. Discounting was not applied due to the study's short time horizon.

2.5.1. Assumptions

For each woman in the trial, we identified relevant screening events and then aggregated the number of events by study arm. To allocate the types and frequency of resource use, we made assumptions regarding screening data since the exact day of the appointment was not available in the Equalscreen data set due to privacy restrictions. For example, if both a cytology and HPV test were reported on the same date, we assumed there was a co-test conducted at a single appointment, which is consistent with the recommendations for this population in the national guidelines [20]. If a histology date was reported on the same date as cytology and/or HPV test, we assumed they were performed at the same gynecology specialist appointment. We also assumed the GP or gynaecologist notified each woman of their screening/biopsy results with associated reimbursement fee.

Gynecology appointments were identified by the presence of histological data, but for some non-histological appointments we did not have information regarding whether women attended screening at their GP or a gynaecologist. These appointments included: i) in-office screeners, ii) HPV-positive self-samplers who attended triage outside the study's management, and iii) HPV-positive self-samplers who attended their scheduled triage appointment (known), but then attended additional follow-up appointments (unknown). We analyzed the trial data using Stata version 17 (StataCorp, College Station, TX, USA).

2.5.2. Cost information

The costs were identified, quantified, and valued through a combination of patient-level data, expert opinion, and national tariffs (Table 1) [22]. All costs were measured in 2020 Norwegian kroner (NOK) and converted to GBP using the average annual 2020 exchange rate (1 NOK = 0.0829 GBP) [23]. Costs were calculated for each arm and stratified into resources required for "primary screening" and "clinical follow-up." Primary screening involved all costs incurred until and including the receival of the screening result from the physician after the first in-office appointment for both in-office screeners and self-sampling screeners. Clinical follow-up involved any further costs after primary screening was complete up until the detection of CIN2+ or end of the observation period. Total costs were determined by adding the primary screening and the clinical follow-up costs. We calculated costs for the extended healthcare perspective in the base-case analysis and the direct healthcare perspective in a scenario analysis. Time and travel costs were taken from a previous study (S1) [22]. In consultation with experts, we made assumptions to quantify the time and travel costs associated with screening/triage events (S1, Table 1).

2.5.3. Analysis

When performing this CEA, we adhered to the CHEERS 2022 reporting checklist [24] (S2). Analysis outcomes from the Equalscreen trial (i.e., number of women screened and number of CIN2+ detected) were used as health benefits. We also calculated total costs, average costs, and incremental cost-effectiveness ratios (ICERs). Screening participation was defined as attending an appointment at a physician or returning a valid self-sample within six months of receiving the reminder letter/invitation. Based on the analysis approach of the previously published Equalscreen trial [7], the outcomes of the trial refer to the total participation of those who screened by i) self-sampling and ii) appointment at a physician, i.e., in-office screeners. The detection of CIN2+ was found through histology results and was used as an endpoint in our analysis, therefore costs for each woman were censored upon detection of CIN2+. CIN2+ detection rates were calculated based on those who participated. To identify the cost drivers of each trial arm, we stratified events into primary screening and clinical follow-up, and then distinguished separate events from one another. Following consultations with decision makers, we estimated multiple outcomes to help inform different aspects of implementing self-sampling or not, but to also inform the choice between different self-sampling strategies. We calculated the average costs i) per invited woman, ii) per screened woman, and iii) per CIN2+ detected. To evaluate the cost-effectiveness of alternative self-sampling delivery approaches, we calculated the ICER, defined as the i) additional cost per additional screened woman, and ii) additional cost per additional CIN2+ detected.

To calculate the ICERs, we first ranked the trial strategies (control, opt-in, and send-to-all) from the least to most costly. ICERs per additional screened woman and per additional CIN2+ detected were calculated for each intervention by dividing the between-strategy cost difference (incremental cost) by the between-strategy difference in number of women screened or CIN2+ detected (incremental effect). The "cost-effective" strategy is not necessarily the strategy with the lowest ICER, as Norwegian policy makers may be willing to pay more for additional health benefits. In standard CEA framework, a strategy is considered cost-effective if its ICER is below the willingness-to-pay threshold for an additional unit of the health benefit. To explore uncertainty, we conducted a sensitivity analysis to evaluate the impact of i) a less expensive self-sample kit, and ii) reducing the time required to perform and return mail a self-sample.

3. Results

The Equalscreen trial [7] reported previously that the total participation rates were 4.8%, 17.0% and 27.7% for the control, opt-in and send-to-all arms, respectively (Table 1). CIN2+ was detected in 1, 12, and 20 women in the control, opt-in, and send-to-all arms, respectively, corresponding to a significant difference in CIN2+ detection of 0.1%, 0.6% and 1.1% of the invited women among the trial arms, and a non-significant difference in CIN2+ detection of 1.1%, 3.7% and 3.8% of the screened women among the trial arms, respectively [7].

3.1. Resource use

From an extended healthcare perspective, similar to the rank-order of participation and CIN2+ detection, the send-to-all arm incurred the highest total cost (86,404 GBP), followed by the opt-in arm (53,082 GBP) and the control arm (21,578 GBP; Table 1). Of the total costs, roughly 88%, 84%, and 91%, respectively, were attributed to primary screening costs. We found that non-histological physician appointments were a cost driver for all trial arms; however, in-office exams contributed relatively less to total costs in the opt-in and send-to-all arms compared with the control arm (Fig. 2, Panel A). For example, non-histological physician appointments contributed to 67% of the total costs in the control arm and ≤ 31% in the self-sampling arms. Similarly, as the number of women returning an HPV-ss increased, the proportional costs increased for HPV lab analyses in the self-sampling arms when compared with the control arm.

The HPV-ss kits costs were the third prominent driver of costs in the self-sampling arms. Due to the direct mailing of the HPV-ss kits in the send-to-all arm, the cost of the self-sample kits was more than two times higher in the send-to-all arm when compared with the opt-in

Table 1
Resources required per screened woman by intervention arm.

			Control ($n = 1892$)			Opt-in ($n = 1897$)			Send-to-all ($n = 1878$)		
	Unit cost (GBP)	Unit cost (GBP)		Costs (GBP)	Costs (GBP)		Costs (GBP)	Costs (GBP)		Costs (GBP)	Costs (GBP)
	Direct healthcare	Time and travel	Units	Direct healthcare	Expanded healthcare	Units	Direct healthcare	Expanded healthcare	Units	Direct healthcare	Expanded healthcare
Primary screening											
Invitation letter[a]	0.26	–	1892	496	496	1897	497	497	–	–	-
Self-sampling kit - returned by inclusion date[b]	5.31	27.11	-	–	-	250	1326	8103	445	2361	14,424
Self-sampling kit - not returned by inclusion date[c]	3.98	–	-	–	-	153	609	609	1433	5702	5702
Reminder letter[d]	0.26	–	-	–	-	1659	435	435	1713	449	449
HPV analysis - self sampling	50.73	–	-	–	-	251[e]	12,734	12,734	448[f]	22,729	22,729
HPV analysis - physician taken	50.73	–	84	4262	4262	87	4414	4414	123	6240	6240
Pap smear cytological analysis	4.31	–	28	121	121	45	194	194	79	341	341
GP appointment - screening	78.26	72.87	-	–	-	11	861	1662	19	1487	2871
Gynaecologist appointment - screening	93.51	72.87	-	–	-	6	561	998	5	468	832
GP/gynaecologist appointment - screening[g]	81.32	72.87	90	7319	13,877	79	6425	12,181	95	7726	14,648
Biopsy histological analysis	39.46	–	-	–	-	8	316	316	26	1026	1026
Gynaecologist appointment - colposcopy/biopsy/screening	177.90	90.94	-	–	-	5	890	1344	19	3380	5108
CervicalScreen Norway informing woman of self-sampling screening result	0.26	–	-	–	-	248[h]	65	65	444[i]	116	116
Reminder letter[j]	0.26	–	-	–	-	6	2	2	11	3	3
Physician informing of screening result[k]	10.61	–	90	955	955	101	1072	1072	138	1464	1464
Total cost of primary screening	-	-	-	13,152	19,711	-	30,399	44,626	-	53,492	75,955
Clinical follow-up											
Pap smear cytological analysis	4.31	–	2	9	9	9	39	39	18	78	78
HPV analysis - physician taken	50.73	–	4	203	203	11	558	558	16	812	812
GP/gynaecologist appointment - screening	81.32	72.87	4	325	617	9	732	1388	14	1139	2159
Biopsy histological analysis	39.46	–	4	158	158	27	1065	1065	28	1105	1105
Gynaecologist appointment - colposcopy/biopsy/screening	177.90	90.94	3	534	807	19	3380	5108	22	3914	5915
Physician informing of screening result[j]	10.61	–	7	74	74	28	297	297	36	382	382
Total cost of clinical follow up	-	-	-	1303	1867	-	6072	8455	-	7429	10,450
Total cost of primary screening + clinical follow up	-	-	-	14,455	21,578	-	36,471	53,082	-	60,921	86,404
Number of invited women	–	–	1892	–	-	1897	–	-	1878	–	-
Cost per invited woman	–	–	-	8	11	-	19	28	-	32	46
Number of screened women	–	–	90	–	-	323	–	-	520	–	-
Cost per screened woman	–	–	-	161	240	-	113	164	-	117	166
Number of CIN2+ detected[l]	–	–	1	–	-	12	–	-	20	–	-
Cost per CIN2+ detected	-	-	-	14,455	21,578	-	3039	4423	-	3046	4320

Costs for each arm are stratified into primary screening and clinical follow-up for both the direct and expanded healthcare perspectives. Total costs and total health benefits are calculated. Average costs are provided for cost per invited woman, cost per screened woman, and cost per CIN2+ detected. Costs converted from 2020 Norwegian kroner (NOK) to 2020 British pounds (GBP), 1 NOK = 0.0829 GBP [23]. Unit costs taken from Groeneveld et al. [22]. Abbreviations: HPV = human papillomavirus, GP = general practitioner, CIN2+ = cervical intra-epithelial neoplasia grade two or worse.

a: Reminder letter for the control arm and a study invitation letter for the opt-in arm, b: Invitation letter, logistics, self-sample equipment. Returned valid self-sample within six months of receiving study invitation, c: Invitation letter, logistics, self-sample equipment. Did not return self-sample within six months of receiving study invitation, d: Study reminder letter - sent to opt-in and send-to-all arms if had not returned a self-sample within three weeks, e: One woman had a self-sample re-analyzed, f: Three women had a self-sample re-analyzed, g: Direct healthcare unit cost is a weighted average (assumes 80% attend GP and 20% attend gynaecologist), h: Two women did not have notification data, i: One woman did not have notification data, j: All attending an appointment at a physician's office were notified of their screening/histology results (assumption), k: HPV positive self-samplers who did not have cytology registered within three months of their scheduled triage appointment were sent a reminder letter to schedule an appointment at their GP; it is possible in-office screeners in need of follow up were sent a reminder letter, but there is no study data regarding this detail, l: Total number of CIN2+ detected.

arm and accounted for roughly seven percentage points more of the total cost. In addition, there was a difference in the percentage of total cost for non-histological physician appointments between the two arms. For example, non-histological physician appointments accounted for roughly seven percentage points more of the total cost in the opt-in arm than in the send-to-all arm. All remaining costs we considered in our analysis contributed to similar percentages of the total cost in each self-sampling arm.

When we restricted costs to the direct healthcare perspective, the total costs were approximately one-third lower due to the exclusions of the women's time and travel costs, but the rank-order of the trial arms remained consistent as well as the distribution of costs between primary screening and clinical follow-up. The percentage of total costs attributed to the non-histological physician appointments and self-sample kits decreased for all arms, while the percentage of total costs attributed to HPV lab analyses increased for all arms (Fig. 2, Panel B).

3.2. Average costs per invited, screened, and CIN2+ detected

From an extended healthcare perspective, the control arm yielded the lowest cost per invited woman (11 GBP), followed by the opt-in arm (28 GBP), and the send-to-all arm (46 GBP) (Table 1). In contrast, we found the opt-in and send-to-all arms yielded a similar cost per screened woman (164 GBP and 166 GBP, respectively), which were nearly 31% lower compared with the control arm (240 GBP). When we estimated the average costs of CIN2+ detection, the send-to-all arm yielded the lowest cost per CIN2+ detected (4320 GBP), followed by the opt-in arm that was 2% higher (4423 GBP) and the control arm which yielded substantially higher average costs to detect one case of CIN2+ (21,578 GBP).

From a direct healthcare perspective, the trial arms held similar rankings for cost per invited woman and cost per screened woman (Table 1). When evaluating the cost per CIN2+ detected, the opt-in

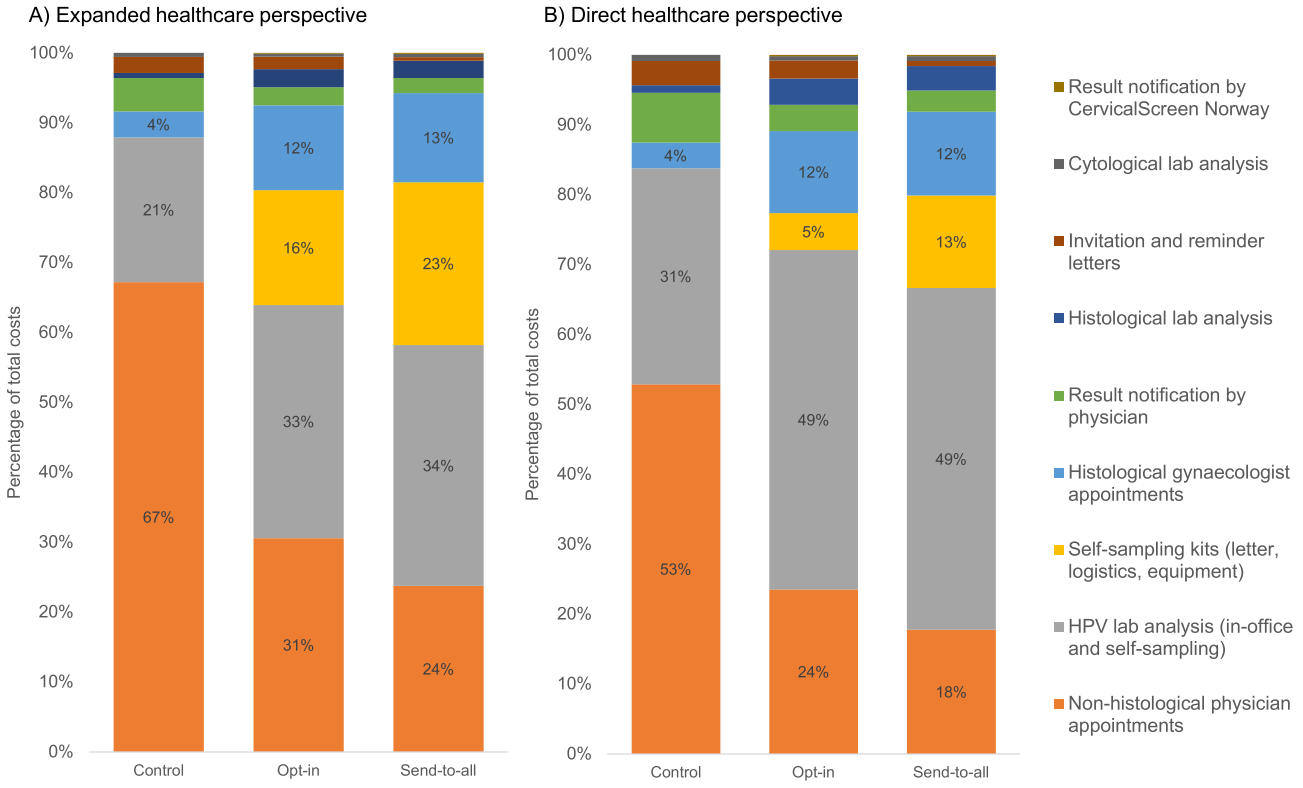

Fig. 2. Drivers of total cost by Equalscreen trial arm.
Total costs include both primary screening costs and clinical follow-up costs evaluated from the extended healthcare (Panel A) and the direct healthcare (Panel B) perspectives. Costs were converted from 2020 Norwegian kroner (NOK) to 2020 British pounds (GBP), 1 NOK = 0.0829 GBP [23]. Abbreviations: HPV = human papillomavirus.

and send-to-all arms continued to yield the lowest but were more similar (3039 GBP and 3046 GBP, respectively) followed by the control arm, which continued to require five times more per screened woman to detect one case of CIN2+ (14,381 GBP).

3.3. Cost-effectiveness analysis

When we assessed both the efficiency and cost outcomes of each strategy in a cost-effectiveness analysis from an extended healthcare perspective, we found that the additional cost per additional screened woman was 135 GBP for the opt-in arm compared with the control arm, and 169 GBP per additional screened woman for the send-to-all arm compared with the opt-in arm (Table 2). The additional cost per additional CIN2+ detected (compared with the next least costly strategy) was 2864 GBP for the opt-in arm and 4165 GBP for the send-to-all arm (Table 2). From a direct healthcare perspective, the ICERs decreased by about 30% for the opt-in arm and about 27% for the send-to-all arm, and the rank-order of the strategies remained consistent (Table 2).

3.4. Sensitivity analysis

When we conducted a one-way sensitivity analysis to evaluate the impact of either lowering the cost of the self-sample kit or decreasing the time required to perform and return a self-sample, we found that from the expanded healthcare perspective, changing these parameters had <10% impact on total costs and the average costs were similar to or slightly lower than the base case (Table 3). The opt-in strategy yielded lower ICERs than the send-to-all strategy for all scenarios, both per additional woman and per additional CIN2+ detected (Table 4), and the rank-order remained consistent with our base case.

Shortening the time to perform and return a self-sample had no impact on direct healthcare costs (Table 3). Under this assumption, lowering the cost of the self-sampling kit reduced total costs by <6% in the opt-in and send-to-all arms, while the control arm was unaffected. The ranking of the arms was consistent with the base case. The average costs showed small fluctuations in rank-order compared to the base case, while the rank-order of the ICERs remained unchanged (Table 4).

Table 2
Summary of the incremental cost-effectiveness ratios (ICERs) per number of screened women and per number of CIN2+ detected by analysis perspective, base case.

	Trial arm	Total cost	Number of screened women	Number of CIN2+ detected	Incremental cost	Incremental number of screened women	Incremental number of CIN2+ detected	ICER: additional cost per additional screened woman	ICER: additional cost per additional CIN2+ detected
Direct healthcare perspective	Control	14,455	90	1	-	–	-	-	-
	Opt-in	36,471	323	12	22,016	233	11	94	2001
	Send-to-all	60,921	520	20	24,450	197	8	124	3056
Expanded healthcare perspective	Control	21,578	90	1	-	-	-	-	-
	Opt-in	53,082	323	12	31,504	233	11	135	2864
	Send-to-all	86,404	520	20	33,323	197	8	169	4165

Arms are ordered from least to most costly in the direct and expanded healthcare perspectives and then incremental cost and incremental health benefits are calculated. The incremental cost is divided by the incremental health benefit to get the corresponding ICER. Costs converted from 2020 Norwegian kroner (NOK) to 2020 British pounds (GBP), 1 NOK = 0.0829 GBP [23]. Abbreviations: CIN2+ = cervical intraepithelial neoplasia grade two or worse, ICER = incremental cost-effectiveness ratio.

Table 3
Sensitivity analyses of key parameters on the total and average costs (GBP) by outcome.

		Control (n = 1892)		Opt-in (n = 1897)		Send-to-all (n = 1878)	
		Direct healthcare	Expanded healthcare	Direct healthcare	Expanded healthcare	Direct healthcare	Expanded healthcare
Base case	Total cost	14,455	21,578	36,471	53,082	60,921	86,404
	Cost per invited woman	8	11	19	28	32	46
	Cost per screened woman	161	240	113	164	117	166
	Cost per CIN2+ detected	14,455	21,578	3039	4423	3046	4320
HPV-ss kit cost lowered to 2.37 GBP	Total cost	14,455	21,578	35,491	52,102	57,310	82,794
	Cost per invited woman	8	11	19	27	31	44
	Cost per screened woman	161	240	110	161	110	159
	Cost per CIN2+ detected	14,455	21,578	2958	4342	2866	4140
HPV-ss time required reduced to 30 minutes	Total cost	14,455	21,578	36,471	50,823	60,921	82,383
	Cost per invited woman	8	11	19	27	32	44
	Cost per screened woman	161	240	113	157	117	158
	Cost per CIN2+ detected	14,455	21,578	3039	4235	3046	4119
HPV-ss time required reduced to 15 minutes	Total cost	14,455	21,578	36,471	48,564	60,921	78,362
	Cost per invited woman	8	11	19	26	32	42
	Cost per screened woman	161	240	113	150	117	151
	Cost per CIN2+ detected	14,455	21,578	3039	4047	3046	3918

Total costs and average costs are calculated for each arm in the direct and expanded healthcare perspectives. The base case is shown in comparison to the scenarios considered in the sensitivity analysis. Costs converted from 2020 Norwegian kroner (NOK) to 2020 British pounds (GBP), 1 NOK = 0.0829 GBP [23]. Abbreviations: CIN2+ = cervical intraepithelial neoplasia grade two or worse.

4. Discussion

The primary Equalscreen trial [7] analysis found that targeting long-term under- and non-screeners with opt-in and send-to-all self-sampling delivery approaches increased screening participation and CIN2+ detection, while our secondary analysis found these delivery approaches also increased the economic costs. The majority of these increased costs were a direct result of the increase in screening participation among the self-sampling arms compared to the control arm and shifted the cost drivers away from office-based resource use to self-sampling resource use (e.g., kit costs and women's time). Compared with a standard reminder letter, HPV-ss enabled a ~ 27% reduction in the cost per screened woman and at least a ~ 79% reduction in the cost per CIN2+ detected. We found that both HPV-ss delivery strategies were considered efficient (i.e., neither was dominated) and either strategy could be considered cost-effective, depending on the decision-makers willingness-to-pay for these short-term outcomes. There are currently no established willingness-to-pay thresholds for our defined short-term health outcomes [25]; therefore, we do not know what decision-makers consider a reasonable relationship between these measured health benefits and their costs. However, a previous economic evaluation presented willingness-to-pay per CIN2+ detected in the Norwegian context [26] and the ICERs for the send-to-all strategy in our analysis were within the ICER ranges found in that evaluation, suggesting send-to-all would be the preferred HPV-ss delivery strategy in Norway. Furthermore, as the severity of a disease is a specific pillar of priority-setting in Norway, i.e., a higher severity warrants a higher willingness-to-pay for health outcomes, the women included in Equalscreen facing a higher risk and down-staged cervical cancers due to infrequent screening, may warrant a higher willingness-to-pay compared with the willingness-to-pay in the analysis targeting the general screening population [26].

Similar to the Equalscreen findings, HPV-ss has been shown to be effective at increasing participation [11,13,27,28] and increasing the

Table 4
Sensitivity analyses of key parameters on the incremental cost-effectiveness ratios (ICERs) per number of screened women and per number of CIN2+ detected by analysis perspective.

		Trial arm	Total cost (GBP)	Number of screened women	Number of CIN2+ detected	Incremental cost (GBP)	Incremental number of screened women	Incremental number of CIN2+detected	ICER: additional cost per additional screened woman (GBP)	ICER: additional cost per additional CIN2+detected (GBP)
HPV-ss kit cost lowered to 2.37 GBP	Direct healthcare perspective	Control	14,455	90	1	-	-	-	-	-
		Opt-in	35,491	323	12	21,036	233	11	90	1919
		Send-to-all	57,310	520	20	21,819	197	8	111	2727
	Expanded healthcare perspective	Control	21,578	90	1	-	-	-	-	-
		Opt-in	52,102	323	12	30,524	233	11	131	2775
		Send-to-all	82,794	520	20	30,692	197	8	156	3836
HPV-ss time required lowered to 30 min	Direct healthcare perspective	Control	14,455	90	1	-	-	-	-	-
		Opt-in	36,471	323	12	22,016	233	11	94	2001
		Send-to-all	60,921	520	20	24,450	197	8	124	3056
	Expanded healthcare perspective	Control	21,578	90	1	-	-	-	-	-
		Opt-in	50,823	323	12	29,245	233	11	126	2659
		Send-to-all	82,383	520	20	31,560	197	8	160	3945
HPV-ss time required lowered to 15 min	Direct healthcare perspective	Control	14,455	90	1	-	-	-	-	-
		Opt-in	36,471	323	12	22,016	233	11	94	2001
		Send-to-all	60,921	520	20	24,450	197	8	124	3056
	Expanded healthcare perspective	Control	21,578	90	1	-	-	-	-	-
		Opt-in	48,564	323	12	26,986	233	11	116	2453
		Send-to-all	78,362	520	20	29,798	197	8	151	3725

ICERs are shown for the direct and expanded healthcare perspectives given the selected sensitivity analysis. Costs converted from 2020 Norwegian kroner (NOK) to 2020 British pounds (GBP), 1 NOK = 0.0829 GBP [23]. Abbreviations: CIN2+ = cervical intraepithelial neoplasia grade two or worse, ICER = incremental cost-effectiveness ratio, HPV-ss = human papillomavirus self-sampling.

detection of CIN2+ [27,29,30] in other settings. To our knowledge, our analysis was the first to evaluate the cost-effectiveness of both opt-in and send-to-all HPV-ss strategies in lieu of standard reminder letters among long-term (10+ years) under- and non-screened women. However, two previous studies compared opt-in vs send-to-all strategies and reported that send-to-all was more likely to be cost-effective [31,32]. In line with our findings, many studies reported that a send-to-all strategy could be cost-effective for different target populations [16,17,30,33–35]. Previous studies also found that altering the costs related to self-sampling kits does not affect results substantially, which is also consistent with our results.

5. Strengths and limitations

The Equalscreen trial was conducted within the already existing national organized screening program in Norway, allowing us to use a reliable estimate of the expected participation rates as the women in the study were actual long-term under- and non-screeners. Our findings, however, may not be generalizable to non-organized settings that may face challenges ensuring high compliance to follow-up recommendations, or settings with different underlying disease burden. In addition, we avoided missing data and attrition by using CervicalScreen Norway's registry data since results from both planned and opportunistic appointments were available. The trial had a randomized design which strengthened the results and provided a more accurate depiction of how different modes of self-sampling are received among long-term under- and non-screeners. The comparison between the self-sampling arms is reliable as both arms were treated with the same protocol (i.e., reminder letters, HPV-ss result information, triage appointment).

There are several limitations to our findings. First, the self-samplers received follow-up beyond the current standard of screening care. If this relatively low cost but high gain follow-up is not implemented alongside HPV-ss, we may have overestimated costs, triage participation rates, and CIN2+ detection, associated with a national implementation. Second, there was a relatively low number of women with CIN2+ detected in this study, which contributes to greater uncertainty in our by-arm comparisons and our cost-effectiveness results. Third, there were women in each arm who attended screening but were not included in the trial because they initiated screening after the six-month window for participation. Data showed that roughly 4% of the control and opt-in arms and 2% of the send-to-all arm participated in primary screening outside the study's required timeframe. It could be expected that under- and non-screeners tend to not respond to screening requests promptly and therefore, a six-month window is not enough time to capture this population's true participation rate. Additional analyses could be performed to determine if expanding the participation inclusion timeframe would alter which self-sampling arm provided the lower economic costs. Finally, the trial data only provided short-term outcomes, therefore we were not able to incorporate eventual treatment and post-treatment costs and health outcomes for CIN2+ women. Further studies are warranted to determine the cost-effectiveness of self-sampling as a strategy in long-term cancer prevention as well as to examine its impact on the number of life years and quality-adjusted life years gained; this projections are possible within a model-based framework, e.g., [36].

6. Implications

Scaling HPV-ss to the entire population of long-term non-screeners in Norway is likely to improve prevention of cervical cancer but would also have important economic implications. In a previous report, there was an estimated 216,000 women who would be eligible for HPV-ss under the Equalscreen inclusion criteria over a 5-year period. If we extrapolate our extended healthcare perspective findings and exclude programmatic costs, opt-in and send-to-all would be expected to cost approximately ~6 million GBP and ~ 10 million GPB, respectively. Furthermore, if every sixth CIN2 or CIN3 treated would prevent a cervical cancer, as previously assumed [11], we estimate that ~150 and ~ 250 cancers could be prevented for the opt-in and send-to-all interventions, respectively, among the 216,000 long-term non-screeners over a 5-year period. Future CEAs conducted from a long-term perspective (using decision-analytic modeling) would be important to consider the long-term health benefits and costs offsets associated with prevented cancers. In addition, extending low-barrier screening methods such as self-sampling to other populations, e.g., all women who have not screened within five years [10], or women who are hesitant/traumatized by gynecological exams, could represent other opportunities to increase coverage. Other countries such as the Netherland, Sweden and recently Australia are providing self-sampling to all women, including routine screeners. A recent cost-effectiveness analysis in Norway [18] has suggested that, provided women comply with recommended follow-up, self-sampling could provide societal cost savings for similar health benefits for the entire screen-eligible population.

7. Conclusions

Our objective was to provide decision makers with information about both the health and economic consequences of opt-in and send-to-all HPV-ss delivery approaches to increase participation among long-term under- and non-screeners in Norway. Although at higher economic costs, we found that the health benefits of directly mailing an HPV-ss test kit to this high-risk population, in lieu of the standard reminder letter, are likely to be considered high-value and cost-effective. However, the preferred HPV-ss delivery approach is ultimately left up to the decision makers and their willingness-to-pay for these health benefits.

Authors' contributions

BTH conceived the original Equalscreen trial. BTH and GA conducted the Equalscreen trial. TK, EAB and BTH contributed to the conceptualization and EAB and TK conceived the current secondary analysis methodology. TK was responsible for formal analyses and visualization. All authors contributed to analysis interpretation. TK wrote the first manuscript draft with support from all authors. All authors commented on drafts and approved the final manuscript. EAB was responsible for supervision. BTH and EAB were responsible for funding acquisition.

Ethics approval and consent to participate

Equalscreen study approval was obtained from the Regional Committees for Medical and Health Research Ethics (2019/111) and Oslo University Hospital's Data Protection Officer (18/14056). A statement regarding the processing of personal data was also obtained from the Data Protection Officer at Akershus University Hospital. For women in self-sampling arms, the invitation included information that by returning the self-sample, they consented to the subsequent procedures described in the invitation letter. All invited women, including those in the control arm, were informed that they could withdraw from the study at any time. The study was performed in accordance with the Declaration of Helsinki.

Data availability

The data contains personal information and the study participants have not consented to public data sharing. Data access requires permission by the relevant Norwegian authorities.

Funding information

The Equalscreen study was funded by the Norwegian Cancer Society (grant number 198073; PI: E.A.B) and Thea Steen Memorial fund (grant number 182687–2016; PI: B.T.H). The funding sources had no role in

study design, data collection and analysis, preparation of the manuscript, or decision to publish. The views expressed in this article are those of the authors and do not necessarily represent the views of the Norwegian Cancer Society.

Declaration of Competing Interest

Authors declare no conflict of interest.

Acknowledgements

We would like to acknowledge Suzanne Campbell for data management support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.10.027.

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