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Three birds with one stone: a protocol for a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening

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ABSTRACT

Introduction

The participation rate is higher in breast cancer screening than in cervical cancer (CCU) and colorectal cancer (CRC) screening. In this cluster-randomised study, we aim to evaluate an intervention offering home-based CCU and CRC screening to women when attending breast cancer screening if they are overdue for CCU and/or CRC screening.

Methods and analysis

On intervention days, one of the five breast cancer screening units in the Central Denmark Region will be randomly allocated to intervention, whereas the remaining units will serve as control. Women attending breast cancer screening in the intervention unit will be offered information regarding their CCU and CRC screening history, and, if overdue, they will be offered self-sampling screening kits. For CCU screening, women aged 50-64 years will be offered a vaginal self-sampling kit for human papillomavirus (HPV) testing. For CRC screening, women aged 50-69 years will be offered a kit to obtain a faecal immunochemical test (FIT). Women attending the control units will receive only standard care.

After the intervention, a questionnaire will be sent to all women in the intervention and control group, asking about their experience while attending breast cancer screening.

Primary outcomes will be difference in the coverage in CCU and CRC screening six months after intervention between the intervention and the control group, and difference in participation rates six months after intervention for those who were overdue for CCU and/or CRC screening at the time of the intervention.

Ethics and dissemination

The project is listed in the record of processing activities for research projects in the Central Denmark Region (R. No.: 1-16-02-217-21). According to the Danish Consolidation Act on Research Ethics Review of Health Research Project, this study was not notifiable to the Committee (R. No.: 1-10-72-1-21). The findings will be disseminated in peer-reviewed scientific journals.

Trial registration number NCT05022511

Strengths and limitations of this study

- To our knowledge, this study will be first of its kind to offer self-sampling kits to women who are overdue for their CCU and CRC screening when attending breast cancer screening
- A strength of this study is the large study population randomly allocated to the intervention or the control group, minimising the risk of confounding
- The study will be conducted within the Danish screening programme. This makes the study design reliable and easy to implement in case of a positive result, while introducing a potential limitation since current national guidelines might be updated, and in this case the study protocol would need to changed accordingly.

INTRODUCTION

Since 2003, the European Union Council has recommended organised, population-based screening for breast cancer, cervical cancer (CCU) and colorectal cancer (CRC) using mammography, cervical cytology or human papillomavirus (HPV) test and guaiac or immunochemical faecal occult blood test (FOBT), respectively,[1]. The three screening programmes have been widely implemented across Europe,[2]. However, most of the screening programmes suffer from sub-optimal participation rates, decreasing their effectiveness. European CRC screening programmes using the faecal immunochemical test (iFOBT, in the following termed FIT) have participation rates of 23-71%,[3]; breast cancer screening programmes, 13-85%,[4]; and CCU screening programmes, 40-85%,[5].

Common strategies to improve participation across the three programmes have been identified at an individual level (e.g. postal or telephone reminders, general practitioner's signature on the invitation letter, education), at a population level (e.g. mass media campaigns) and at the health service management level (e.g. scheduled appointments, mobile mammography, HPV self-sampling),[6-8]. Despite such initiatives, participation in cancer screening is often suboptimal.

In Denmark, the participation rate in breast cancer screening exceeds 80%,[9], which is above the 61% share recorded for CCU screening,[10] and CRC screening,[11]. Thus, attending breast cancer screening provides an opportunity for personal communication with the women regarding their screening status in CRC and CCU programmes. Furthermore, a UK study revealed that women are potentially interested in this approach,[12]. However, it has yet to be explored whether this holds potential to increase participation in the two screening programmes with the lowest participation rates.

The aim of this study will be to increase participation in CCU and CRC screening programmes in Denmark by offering home-based CCU and CRC screening to women attending breast cancer screening if they are overdue for one or both screening programmes.

METHODS AND ANALYSIS

Setting

In Denmark, women aged 50-69 years are entitled to biennial breast cancer screening by mammography. The women receive a digital invitation with a pre-booked appointment at a screening unit,[13]. If the woman fails to attend the pre-booked appointment, a reminder is sent shortly after.

Women aged 23-64 years are offered CCU screening. From the age of 50 years, they receive an invitation every fifth year via digital mail encouraging them to book an appointment with their general practitioner (GP) to have a cervical cytology sample taken. Non-participants receive up to two reminders three and six months after the initial invitation.

All residents aged 50-74 years are offered biennial screening for CRC with FIT. They receive a kit for self-sampling by mail including written instructions and pictograms explaining how to collect the sample, an informational pamphlet and a pre-paid, pre-addressed return envelope to return the sample. A reminder is sent six weeks after the initial invitation if no sample has been examined.

In all three screening programmes, non-participants receive a new invitation if they remain in the screening-eligible age range when due for screening again, unless they have actively unsubscribed from the programme.

In Denmark, five regions manage primary and secondary healthcare services, which are tax-funded, free-access services for all residents. The Central Denmark Region accounts for approximately 1.3 million inhabitants corresponding to roughly one fourth of the Danish population,[14]. The three population-based cancer screening programmes are based on national guidelines and administered in each of the five regions.

Communication between residents and public authorities, including the healthcare systems, is mainly through secure, digital mail, whereas residents with exemptions from digital mail receive surface mail. This group accounts for 6.3% of the Danish population in the age range from 45 years to 75 years,[15].

Study design

The study will be a cluster-randomised controlled trial conducted in the Central Denmark Region where five breast cancer screening units serve women five days a week. All five units will be included in the study and will be randomised to an equal amount of intervention days. On the intervention days, the other four units will serve as the control group, providing a randomisation ratio of 1:4 (Figure 1). Randomisation will be conducted by a data manager using a pseudorandom number function in the statistical software STATA V. 16.
The study will comply with the SPIRIT statement,[16].

Study population

The population will comprise women aged 50-69 years attending breast cancer screening in the Central Denmark Region on intervention days. The study will include women invited for breast cancer screening at 69 years who, due to postponement, have turned 70 years at their appointment.
In CCU screening, women aged 50-64 years will be classified as overdue if they have never participated, if they have no record of a cervical sample in the past five years and six months, or if they were non-responders to a screening invitation received more than six months ago.
In CRC screening, women aged 50-69 years will be classified as overdue if they have no record of a FIT in the past two years and 4.5 months, or if they have not responded to an invitation received more than 4.5 months ago. The time intervals were chosen to ensure that the women have had time to receive both an invitation and the first reminder without responding after a three-month interval.

Intervention

Figure 2 summarises the intervention. On intervention days, a research assistant will be available in one of the five screening units in the Central Denmark Region, asking women attending breast cancer screening if they are interested in having a check-up on their CCU and CRC screening status. If oral consent is obtained, the research assistant will check their screening status in the administrative register of each of the screening programmes.

Women who are overdue for CCU screening will be offered to receive a self-sampling kit by mail or reminded to call their GP to have a cervical cytology sample taken, depending on their preference. If a woman prefers a self-sampling kit, she will receive a dry brush for vaginal self-sampling (Evalyn Brush from Rovers Medical Devices, Netherlands),[17, 18], written and picture-based user instructions on how to collect the sample, the national information pamphlet for CCU screening, and a pre-paid, pre-addressed envelope for returning the sample. A reminder will be sent six weeks after dispatch of the self-sampling kit if no sample has been returned. The vaginal self-samples will be analysed for high-risk HPV (HPV16, HPV18 and 12 other high-risk HPV types in one pool; HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) using the Cobas 4800 HPV DNA test (Roche Diagnostics, Switzerland),[19] at the Department of Pathology, Randers Regional Hospital, according to routine laboratory protocols. Follow-up will be according to nationally decided procedures.

In the national CRC screening programme, everyone who is overdue for CRC screening may order a new screening kit. If a woman in the present study is overdue for CRC screening, we offer to order a new self-sampling kit for her, which she will then receive by mail. The package sent to her will contain a self-sampling kit for FIT (OC Sensor System, Eiken Chemical Company, Japan), instructions on how to collect a sample, the national information pamphlet for CRC screening and a pre-paid, pre-addressed return envelope. A reminder will be sent six weeks after dispatch of the self-sampling kit if no sample has been returned. The samples will be analysed for haemoglobin with a cut-off value of 100 ng haemoglobin (HB)/mL buffer. Follow-up will be conducted according to the standard procedure in the national CRC screening programme.

If the woman accepts a self-sampling kit for CCU and/or CRC screening, she will be informed - orally at the breast cancer screening unit and in the written material - that she will subsequently receive the result of the test(s) by digital mail, and a copy of the result will be sent to her GP.

The women in the control group receive only the standard screening offers forming part of the national screening programmes.

The women in the study population will receive a survey within few days after having attended breast cancer screening asking about their experience with breast cancer screening. The survey will include questions on their general experience with the visit attended in the screening unit. Additionally, the women in the intervention group will be asked if they find it acceptable to be asked about participation in the two other screening programmes when attending their breast cancer screening visit.

Clinical management

If a woman returns a vaginal self-sample for HPV testing, she and her GP will receive the result of her test by digital mail within three weeks after the completed test has been returned. If the sample is HPV positive, the woman will be advised to see her GP within one month for an additional gynaecologic examination at which a cervical cytology sample is collected. The GP-collected sample will be analysed for HPV, undergo microscopy and will be classified according to the Bethesda System,[20]. The GP is responsible for further clinical management according to national screening guidelines. If no cervical sample from a HPV-positive woman has been examined after 90 days, one reminder to book an appointment at the GP will be sent by digital mail.

If the self-sample is HPV negative, follow-up will be conducted according to age and screening history. HPV-negative women aged 50-59 years will be referred back to the national screening

programme. Women aged 60-64 years who have a normal cervical sample within the past six years will exit the screening programme. Women aged 60-64 years without a normal cervical sample within the past six years will be re-invited within 12 months to do an additional self-sample for HPV before they exit the programme. If the self-sample is invalid, the woman will be advised to see her GP for a cervical sample.

If the woman returns a self-collected FIT, she will receive the result by digital mail and the GP will also receive the result within two weeks from returning the completed sample. Follow-up is conducted according to the national screening programme,[21]. Thus, if the FIT is positive for traces of blood, the woman will be contacted by surface mail with a pre-booked appointment for colonoscopy within 14 days at a hospital-based screening endoscopy unit. If the woman does not show up for the colonoscopy, she will be reminded twice by digital mail and once by telephone with advice to book a new appointment. If the FIT is negative, the woman will be referred back to the national screening programme through a new invitation sent out two years later. If the test is invalid, a new test kit is sent to the woman.

Since the study is nested within national cancer screening programmes, the clinical management strategies used in the study must adhere to national guidelines. If the current national guidelines are updated during the study period, details relating to the study may be changed accordingly, and the project leader will be responsible for passing on the information to relevant partners.

Outcomes

Main effect measures

1) Difference between the control and the intervention group in overall coverage of CCU/CRC screening six months after the visit in the breast cancer screening unit.

This will be measured as the proportion of women adherent with CCU/CRC screening in the intervention group compared with the control group.

2) Difference between the control and the intervention group with respect to CCU/CRC screening participation six months after the intervention for the women who are overdue for CCU/CRC screening at the intervention date.

Secondary outcomes

Among the women who are overdue for CCU screening, the secondary outcomes will be prevalence of HPV in vaginal self-samples, compliance with follow-up in HPV-positive women (timely follow-up will be reported as a GP-collected cervical sample within 180 days from the HPV-positive sample), screening history of self-samplers ("under-screened" defined as screened at least once with a cytology sample within the ten years leading up to the inclusion date, but not screened within the past five years and six months, "un-screened" defined as no cytology sample registered within the past ten years), referral rate for colposcopy, incidence of cervical intraepithelial neoplasia of grade 2+ (CIN2+) (including CIN2, CIN3/adenocarcinoma in situ (AIS) and carcinoma), incidence of HPV-positive cases in women 60-64 years after 12 months with an initial negative HPV sample.

For those who are overdue for CRC screening, secondary outcomes will be prevalence of positive FIT cases, compliance with follow-up (timely follow-up will be reported as colonoscopy within 60 days from a positive FIT), screening history of women who receive a new FIT ("under-screened" defined as a minimum of one FIT, but no FIT within the past two years and 4.5 months, "un-screened" defined as no previous FIT despite invitation) histology (adenomas and cancer).

Participation after subsequent screening invitation in all three cancer screening programmes five years after the intervention may be measured.

Process outcomes

In the intervention group, process outcomes will be the proportion of women accepting a check-up on their CCU and CRC screening status, the proportion of women overdue for CCU

and/or CRC screening, the proportion of women accepting a test-kit and the proportion of women not returning the kit.

The surveys sent to the women after inclusion will be used to evaluate the acceptability of the intervention and the participants' satisfaction with the breast cancer screening.

Other variables

Outcomes to test if the randomisation succeeded will be screening history, previous cancer diagnoses, hysterectomy, inflammatory bowel disease (IBD) and socioeconomic data (age, ethnicity, marital status and educational level).

Sample size

Preliminary data from a study of the proportion of women participating in one, two or all three Danish cancer screening programmes show that approximately 20% of women participating in breast cancer screening did not participate in CCU screening (excluding women with hysterectomy or a Charlson comorbidity score ≥ 3), and approximately 35% did not participate in CRC screening (excluding women with a previous diagnosis of colorectal cancer or a Charlson comorbidity score ≥ 3) (unpublished data).

The premise is to attend each breast cancer screening unit 20 times, corresponding to a total of 100 intervention days. Every unit has pre-booked approximately 74 women daily of whom 55 are expected to attend. Assuming that 40 women per day are eligible for CCU screening and 52 for CRC screening, the study may detect a difference in screening coverage as low as 2.3% in CCU screening (increasing from 80% to 82.3%) and 2.4% in CRC screening (increasing from 65% to 67.4%) with a risk of type 1 error of 5% and type 2 error of 10% (power of 90%).

A design effect due to cluster randomisation is not taken into account as the intervention will be equally distributed between the screening units over the entire study period. The individuals within the clusters are considered independent of each other,[22].

Enrolment was initiated in September 2021.

Data sources

The study population will be identified in the regional administrative system of the breast cancer screening programme. On intervention days, the current status of participation in CCU screening will be obtained from the Danish Pathology Register (DPR), which holds data on cervical cytology samples in Denmark,[23]. Furthermore, the current status of participation in CRC screening will be obtained from the Invitation and Administration Module (IAM), which holds data on FIT in Denmark.

Data on test results from cytology, HPV test, colposcopies and screening history in CCU screening will be retrieved from the DPR and the Danish CCU Screening Database,[24]. Data on screening history in CRC screening and data on FIT result, colonoscopies and histology will be retrieved from the Danish CRC Screening Database,[25].

Furthermore, data on previous cancer diagnoses will be drawn from The Danish Cancer Registry,[26] and The Danish National Patient Register,[27] which will also provide data on IBD and total hysterectomies (codes are provided in Table 1),[28].

Table 1 International Classification of Diseases (ICD) codes used to identify previous cancer diagnoses, total hysterectomies and irritable bowel disease

	ICD-7/8	**ICD-10**
Colorectal cancer	153.x, 154.x, 253.x, 453.x, 454.x, 653.x, 654.x, 753.x, 754.x, 853.x, 854.x;	C18-20
Cervical cancer	171.x, 671.x, 771.x, 871.x;	C53
Hysterectomy	ICD-8 (1977-1995) surgical procedure codes: opr61050, opr61020, opr72230, opr61040, opr72650, opr61100, opr72240, opr61780, opr62300	ICD-10 surgical procedure codes: KLCD00, KLCD01, KLCD04, KLCD10, KLCD11, KLCD30, KLCD31, KLCD40, KLCD96, KLCD97, KLDC10, KLDC13, KLDC96, KLDC20, KLDC23, KZXX00, KMCA33, KLEF13, KLEF00B
Irritable bowel disease		DK50-51

Note: Danish Cancer Register used ICD-7, Danish National Patient Register used ICD-8.

Statistics Denmark will provide sociodemographic data,[29]. Using Statistics Denmark's classification, ethnicity will be categorised by country of origin as either Danish, Western (EU, Andorra, Australia, Canada, Iceland, Liechtenstein, Monaco, New Zealand, Norway, San Marino, Switzerland and the USA) or non-Western (others). Marital status will be classified as cohabitating or living alone. Highest educational attainment will be classified according to UNESCO's classification as low (≤ 10 years), middle (11–15 years) or higher education (> 15 years).

The study cohort will be managed in REDCap, which is a secure web application for building and managing online surveys and databases,[30]. All data will be linked at the individual level using the unique ten-digit CPR number assigned in Denmark at birth or upon emigration,[26].

Statistical analyses

Baseline characteristics in both groups will be presented using descriptive statistics (number and proportions) to determine if the randomisation was equally balanced.

Differences in coverage and participation rates between the intervention and the control group will be estimated both as absolute difference and relative risk with 95% confidence intervals (CIs).

Secondary and process outcomes will be reported by descriptive statistics including 95% CIs.

All statistical analyses will be conducted using STATA V. 16.

Patient and public involvement

The study design was pilot tested for feasibility and acceptability, the latter including women attending the breast cancer screening unit at the days of pilot testing. These women were asked to share their experience with the intervention. The responses were analysed to ensure participant satisfaction with the intervention. Other than this, neither patients nor the public will be involved in this research. We plan to disseminate the results to the general screening population and patient organisations through mass media.

ETHICS AND DISSEMINATION

According to the EU's General Data Protection Regulation (Article 30), this project is listed in the record of processing activities for research projects in the Central Denmark Region (R. No.: 1-16-02-217-21). Under the Consolidation Act on Research Ethics Review of Health Research Projects, Consolidation Act number 1083 of 15 September 2017, Section 14 (2), notification of medical database research projects to the research ethics committee system is required only if the project involves human biological material. Thus, this study was not notifiable to the

Committee (R. No.: 1-10-72-1-21). Accordingly, information may be retrieved from regional administrative systems and registers without informed consent from the participants when approved by the hospital management. The hospital management at Randers Regional Hospital, Central Denmark Region, has approved this project. The study is registered with clinicaltrials.gov (R. No. NCT05022511) (see Table 2 for the World Health Organization Trial Registration Data Set) and will be conducted in accordance with the Good Clinical Practice Guidelines.

The results will be reported in international peer-reviewed scientific journals and compiled as a thesis, which will be submitted for examination for a PhD at Aarhus University, Denmark. Furthermore, results will be presented at national and international scientific meetings and disseminated to healthcare stakeholders, patient organisations and the general public through press releases.

Table 2 All items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05022511
Date of registration in primary registry	10 August, 2021
Secondary identifying numbers	N/A
Source(s) of monetary or material support	The University Research Clinic in Cancer Screening and the Department of Public Health Programmes, Randers Regional Hospital, Denmark
Primary sponsor	The Department of Public Health Programmes and the University Clinic in Cancer Screening, Randers Regional Hospital, Denmark
Secondary sponsor(s)	Department of Clinical Medicine, Aarhus University, Denmark
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Contact for scientific queries	Anne Dorte Lerche Helgestad, MD Department of Public Health Programmes and University Clinic in Cancer Screening, Randers Regional Hospital, Denmark
Public title	Three birds with one stone
Scientific title	Three birds with one stone: a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	Cervical cancer and colorectal cancer screening
Intervention(s)	Active comparator: An offer to receive information on screening status in cervical and colorectal cancer screening when attending breast cancer screening. If overdue for one or both screening programmes, self-sampling screening test(s) is/are offered.

Data category	Information
	Control comparator: Standard screening offers according to the national screening programmes
Key inclusion and exclusion criteria	Ages eligible for study: 50-64 years (cervical cancer screening), 50-69 years (colorectal cancer screening) Sexes eligible for study: women Accepts healthy volunteers: no
	Inclusion criteria: women aged 50-69 years booked for a breast cancer screening on an intervention day
	Exclusion criteria: Not eligible for cervical or colorectal cancer screening, did not attend breast cancer screening, changed appointment for breast cancer screening after randomisation, insufficient Danish skills to provide informed consent
Study type	Interventional
	Allocation: cluster randomised intervention model. Parallel assignment 1:4.
	Primary purpose: prevention
Date of first enrollment	September 2021
Target sample size	37,000
Recruitment status	Recruiting
Primary outcome(s)	1) Difference between intervention and control group with respect to coverage in cervical cancer/colorectal cancer screening six months after the intervention. 2) Difference between the intervention and the control group in proportion of women participating in cervical cancer and colorectal screening after six months for women who were overdue for their cervical cancer/colorectal cancer screening at the intervention.
Key secondary outcomes	For both cervical and colorectal cancer screening, secondary outcomes will be screening-related outcome, clinical follow-up, satisfaction with breast cancer screening during intervention and process outcomes.

PERSPECTIVES

To our knowledge, this study will be the first of its kind to offer an inter-programme collaboration between three cancer screening programmes simultaneously by reaching out to women overdue for CRC and/or CCU screening when participating in breast cancer screening. By reducing logistic challenges and taking advantage of a more personalised communication with the women, this study may enhance participation in un- and under-screened women who have not deliberately chosen not to participate. These women are presumably susceptible to preventive healthcare but for a host of reasons end up as non-participants.

A strength of this study is that it is an easily scalable intervention, which - in case of a positive result – has the potential to be implemented in the national screening programme at the breast cancer screening units without great costs.

Contributorship statement

ADLH is the principal investigator of the study and responsible for the coordination of the trial with supervision from MBL and BA. ADLH, MBL and BA are primarily responsible for the study design with input from SN, MT and LKP.

MT and LKP contributed advice and knowledge on CCU screening, follow-up after CCU screening and self-sampling. SN contributed advice and knowledge on CRC screening, follow-up after CRC screening and statistical considerations.

ADLH drafted the manuscript. All authors contributed with further development of the manuscript and reviewed and approved the final version.

Competing interests

Roche Diagnostics sponsors the Cobas 4800 HPV DNA tests. According to the contract between Roche Diagnostics and the University Research Clinic for Cancer screening, the Department of Public Health Programmes, Randers Regional Hospital, Roche Diagnostics has no influence on the scientific process and no editorial rights pertaining to this manuscript. MT, LKP and BA have participated in other studies with HPV DNA tests sponsored by Roche Diagnostics. MT has received honoraria from Roche Diagnostics for lectures on HPV self-sampling. SN has received a speaking fee from Norgine and LKP has received speakers fee from Astra Zeneca and MSD.

Data availability statement

Under Danish law, restrictions will apply to the availability of the data generated during this study. Register data will be used under a license for the present study and may be available upon reasonable request to the Danish Health Data Authority and Statistics Denmark. The participants will not be asked to provide consent for publication of the questionnaire data, but

data may be available in anonymous form from the corresponding author upon reasonable request.

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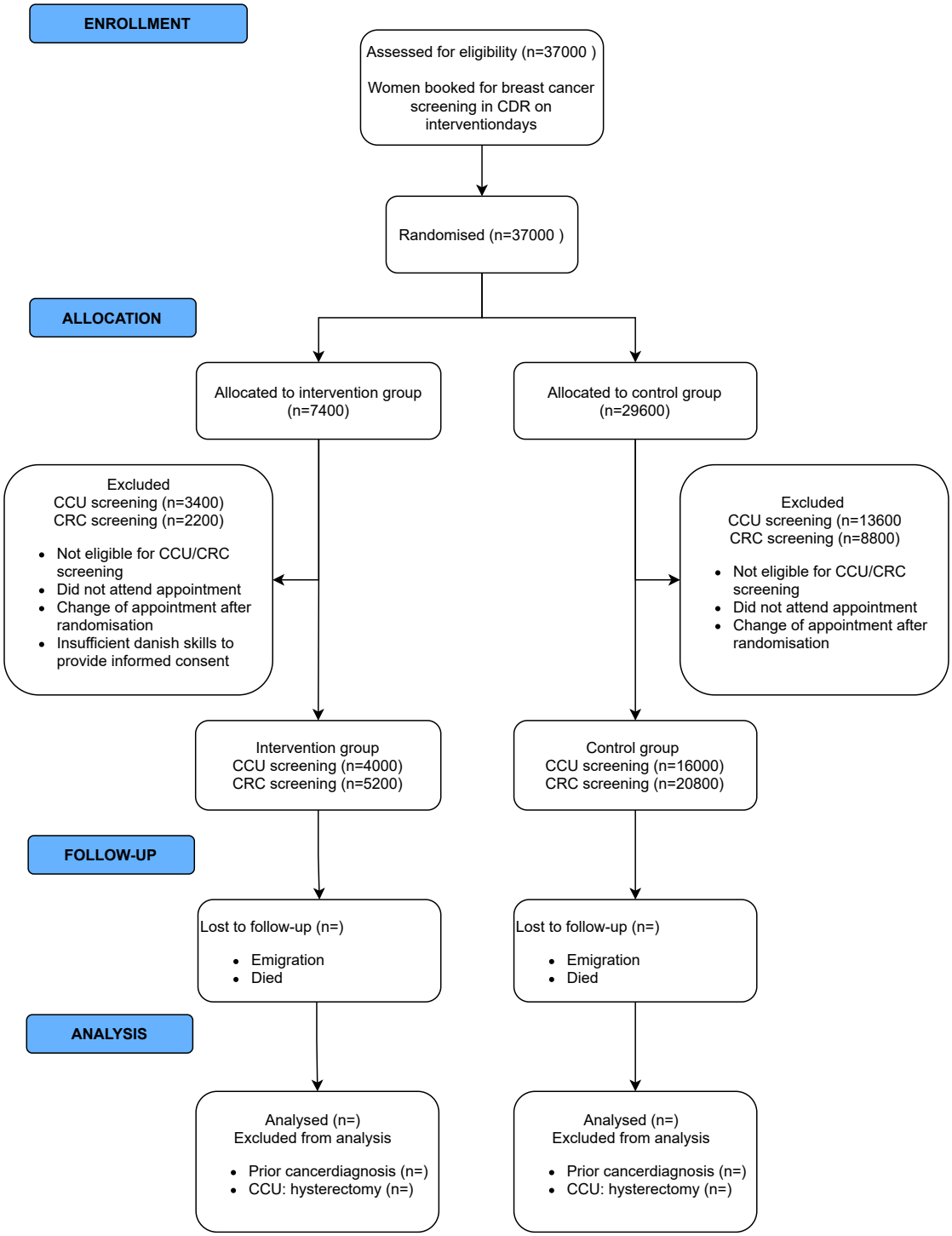
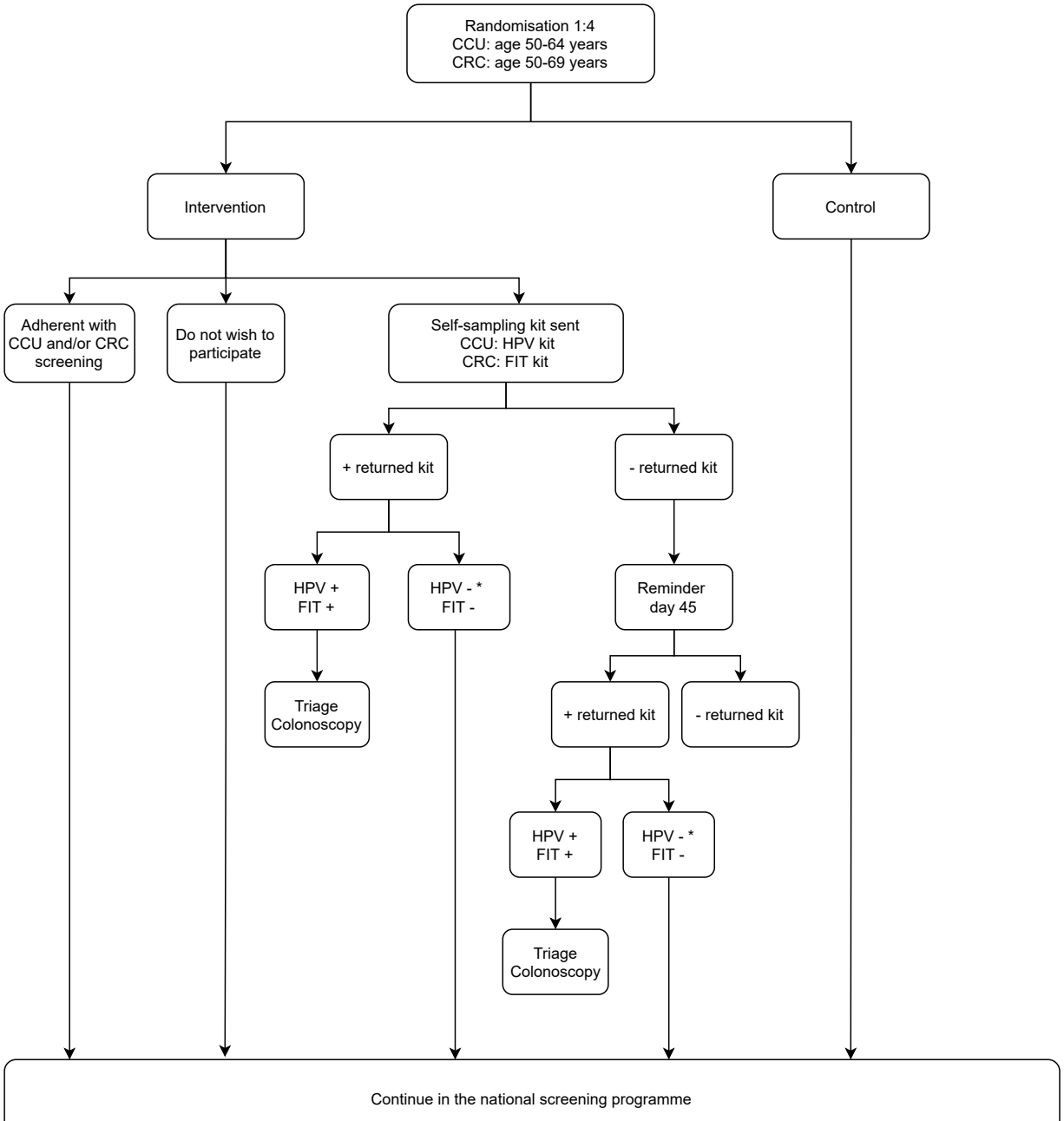
Figure 1 CONSORT 2010 flow diagram of the study

Figure 2 Flow diagram of the intervention


ENROLLMENT
Assessed for eligibility (n=37000)
Women booked for breast cancer screening in CDR on interventiondays
Randomised (n=37000)
ALLOCATION
Allocated to intervention group (n=7400)
Allocated to control group (n=29600)
Excluded
CCU screening (n=3400)
CRC screening (n=2200)
Not eligible for CCU/CRC screening
Did not attend appointment
Change of appointment after randomisation
Insufficient danish skills to provide informed consent
Excluded
CCU screening (n=13600
CRC screening (n=8800)
Not eligible for CCU/CRC screening
Did not attend appointment
Change of appointment after randomisation
Intervention group
CCU screening (n=4000)
CRC screening (n=5200)
Control group
CCU screening (n=16000)
CRC screening (n=20800)
FOLLOW-UP
Lost to follow-up (n=)
Emigration
Died
Lost to follow-up (n=)
Emigration
Died
ANALYSIS
Analysed (n=)
Excluded from analysis
Prior cancerdiagnosis (n=)
CCU: hysterectomy (n=)
Analysed (n=)
Excluded from analysis
Prior cancerdiagnosis (n=)
CCU: hysterectomy (n=)


Randomisation 1:4
CCU: age 50-64 years
CRC: age 50-69 years
Intervention
Control
Adherent with CCU and/or CRC screening
Do not wish to participate
Self-sampling kit sent
CCU: HPV kit
CRC: FIT kit
+ returned kit
- returned kit
HPV + FIT +
HPV - * FIT -
Reminder day 45
Triage Colonoscopy
+ returned kit
- returned kit
HPV + FIT +
HPV - * FIT -
Triage Colonoscopy
Continue in the national screening programme
*Women aged 60-64 years will receive a new self-sampling kit in one year

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15, table 2
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16, 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	N/A

		management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9, figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods:			
Assignment of			

interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A No blinding

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to	12,15

		promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A The trial is with minimal risks and of short duration; hence it has been decided that there will be no need for a DMC

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A No interim analysis will be made.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8, 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14, 17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Three birds with one stone: a protocol for a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening

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Three birds with one stone: a protocol for a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening

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ABSTRACT

Introduction

The participation rate is higher in breast cancer screening than in cervical cancer (CCU) and colorectal cancer (CRC) screening. In this cluster-randomised study, we aim to evaluate an intervention offering home-based CCU and CRC screening to women when attending breast cancer screening if they are overdue for CCU and/or CRC screening.

Methods and analysis

On intervention days, one of the five breast cancer screening units in the Central Denmark Region will be randomly allocated to intervention, whereas the remaining units will serve as control. Women attending breast cancer screening in the intervention unit will be offered information regarding their CCU and CRC screening history, and, if overdue, they will be offered self-sampling screening kits. For CCU screening, women aged 50-64 years will be offered a vaginal self-sampling kit for human papillomavirus (HPV) testing. For CRC screening, women aged 50-69 years will be offered a kit to obtain a faecal immunochemical test (FIT). Women attending the control units will receive only standard care.

After the intervention, a survey will be sent to all women in the intervention and control group, asking about their experience while attending breast cancer screening.

Primary outcomes will be difference in the coverage in CCU and CRC screening six months after intervention between the intervention and the control group, and difference in participation rates six months after intervention for those who were overdue for CCU and/or CRC screening at the time of the intervention.

Ethics and dissemination

The project is listed in the record of processing activities for research projects in the Central Denmark Region (R. No.: 1-16-02-217-21). According to the Danish Consolidation Act on Research Ethics Review of Health Research Project, this study was not notifiable to the Committee (R. No.: 1-10-72-1-21). The findings will be disseminated in peer-reviewed scientific journals.

Trial registration number NCT05022511

Strengths and limitations of this study

- To our knowledge, this study will be first of its kind to offer self-sampling kits to women who are overdue for their CCU and CRC screening when attending breast cancer screening
- A strength of this study is the large study population randomly allocated to the intervention or the control group, minimising the risk of confounding
- The study will be conducted within the Danish screening programme. This makes the study design reliable and easy to implement in case of a positive result, while introducing a potential limitation since current national guidelines might be updated, and in this case the study protocol would need to changed accordingly.

INTRODUCTION

Since 2003, the European Union Council has recommended organised, population-based screening for breast cancer, cervical cancer (CCU) and colorectal cancer (CRC) using mammography, cervical cytology or human papillomavirus (HPV) test and guaiac or immunochemical faecal occult blood test (FOBT), respectively [1]. The three screening programmes have been widely implemented across Europe [2]. However, most of the screening programmes suffer from sub-optimal participation rates, decreasing their effectiveness. European CRC screening programmes using the faecal immunochemical test (iFOBT, in the following termed FIT) have participation rates of 23-71% [3]; breast cancer screening programmes, 13-85% [4]; and CCU screening programmes, 40-85% [5].

Common strategies to improve participation across the three programmes have been identified at an individual level (e.g. postal or telephone reminders, general practitioner's signature on the invitation letter, education), at a population level (e.g. mass media campaigns) and at the health service management level (e.g. scheduled appointments, mobile mammography, HPV self-sampling) [6-8]. Despite such initiatives, participation in cancer screening is often suboptimal.

In Denmark, the participation rate after invitation in breast cancer screening exceeds 80% [9], which is above the 61% recorded for both CCU [10] and CRC screening [11].Thus, attending breast cancer screening provides an opportunity for personal communication with the women regarding their screening status in CRC and CCU programmes. Furthermore, a UK study revealed that women are potentially interested in this approach [12]. However, it has yet to be explored whether this holds potential to increase participation in the two screening programmes with the lowest participation rates.

The aim of this study will be to increase participation in CCU and CRC screening programmes in Denmark by offering home-based CCU and CRC screening to women attending breast cancer screening if they are overdue for one or both screening programmes.

METHODS AND ANALYSIS

Setting

In Denmark, women aged 50-69 years are entitled to biennial breast cancer screening by mammography. The women receive a digital invitation with a pre-booked appointment at a screening unit [13]. If the woman fails to attend the pre-booked appointment, a reminder is sent shortly after.

Women aged 23-64 years are offered CCU screening. From the age of 50 years, they receive an invitation every fifth year via digital mail encouraging them to book an appointment with their general practitioner (GP) to have a cervical cytology sample taken. Non-participants receive up to two reminders three and six months after the initial invitation.

All residents aged 50-74 years are offered biennial screening for CRC with FIT. They receive a kit for self-sampling by mail including written instructions and pictograms explaining how to collect the sample, an informational pamphlet and a pre-paid, pre-addressed return envelope to return the sample. A reminder is sent six weeks after the initial invitation if no sample has been examined.

In all three screening programmes, non-participants receive a new invitation if they remain in the screening-eligible age range when due for screening again, unless they have actively unsubscribed from the programme.

In Denmark, five regions manage primary and secondary healthcare services, which are tax-funded, free-access services for all residents. The Central Denmark Region accounts for approximately 1.3 million inhabitants corresponding to roughly one fourth of the Danish population [14]. The three population-based cancer screening programmes are based on national guidelines and administered in each of the five regions.

Communication between residents and public authorities, including the healthcare systems, is mainly through secure, digital mail, whereas residents with exemptions from digital mail receive surface mail. This group accounts for 6.3% of the Danish population (both sexes) in the age range from 45 years to 75 years [15].

Study design

The study will be a cluster-randomised controlled trial conducted in the Central Denmark Region where five breast cancer screening units serve women five days a week. All five units will be included in the study and will be randomised to an equal amount of intervention days. On the intervention days, the other four units will serve as the control group, providing a randomisation ratio of 1:4 (Figure 1). Randomisation will be conducted by a data manager using a pseudorandom number function in the statistical software STATA V. 16.
The study will comply with the SPIRIT statement [16].

Study population

The population will comprise women aged 50-69 years attending breast cancer screening in the Central Denmark Region on intervention days. The study will include women invited for breast cancer screening at 69 years who, due to postponement, have turned 70 years at their appointment.
In CCU screening, women aged 50-64 years will be classified as overdue if they have never participated, if they have no record of a cervical sample in the past five years and six months, or if they were non-responders to a screening invitation received more than six months ago.
In CRC screening, women aged 50-69 years will be classified as overdue if they have no record of a FIT in the past two years and 4.5 months, or if they have not responded to an invitation received more than 4.5 months ago. The time intervals were chosen to ensure that the women have had time to receive both an invitation and the first reminder without responding after a three-month interval.

Intervention

Figure 2 summarises the intervention. On intervention days, a research assistant will be available in one of the five screening units in the Central Denmark Region, asking women attending breast cancer screening if they are interested in having a check-up on their CCU and CRC screening status. If oral consent is obtained, the research assistant will check their screening status in the administrative register of each of the screening programmes.

Women who are overdue for CCU screening will be offered to receive a self-sampling kit by mail or reminded to call their GP to have a cervical cytology sample taken, depending on their preference. If a woman prefers a self-sampling kit, she will receive a dry brush for vaginal self-sampling (Evalyn Brush from Rovers Medical Devices, Netherlands) [17, 18], written and picture-based user instructions on how to collect the sample, the national information pamphlet for CCU screening, and a pre-paid, pre-addressed envelope for returning the sample. A reminder will be sent six weeks after dispatch of the self-sampling kit if no sample has been returned. The vaginal self-samples will be analysed for high-risk HPV (HPV16, HPV18 and 12 other high-risk HPV types in one pool; HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) using the Cobas 4800 HPV DNA test (Roche Diagnostics, Switzerland),[19] at the Department of Pathology, Randers Regional Hospital, according to routine laboratory protocols. Follow-up will be according to nationally decided procedures.

In the national CRC screening programme, everyone who is overdue for CRC screening may order a new screening kit. If a woman in the present study is overdue for CRC screening, we offer to order a new self-sampling kit for her, which she will then receive by mail. The package sent to her will contain a self-sampling kit for FIT (OC Sensor System, Eiken Chemical Company, Japan), instructions on how to collect a sample, the national information pamphlet for CRC screening and a pre-paid, pre-addressed return envelope. A reminder will be sent six weeks after dispatch of the self-sampling kit if no sample has been returned. The samples will be analysed for haemoglobin with a cut-off value of 100 ng haemoglobin (HB)/mL buffer. Follow-up will be conducted according to the standard procedure in the national CRC screening programme.

If the woman accepts a self-sampling kit for CCU and/or CRC screening, she will be informed - orally at the breast cancer screening unit and in the written material - that she will subsequently receive the result of the test(s) by digital mail, and a copy of the result will be sent to her GP.

The women in the control group receive only the standard screening offers forming part of the national screening programmes.

The women in the study population will receive a survey within few days after having attended breast cancer screening asking about their experience with breast cancer screening. The survey will include questions on their general experience with the visit attended in the screening unit. Additionally, the women in the intervention group will be asked if they find it acceptable to be asked about participation in the two other screening programmes when attending their breast cancer screening visit.

Clinical management

If a woman returns a vaginal self-sample for HPV testing, she and her GP will receive the result of her test by digital mail within three weeks after the completed test has been returned. If the sample is HPV positive, the woman will be advised to see her GP within one month for an additional gynaecologic examination at which a cervical cytology sample is collected. The GP-collected sample will be analysed for HPV, undergo microscopy and will be classified according to the Bethesda System [20]. The GP is responsible for further clinical management according to national screening guidelines. If no cervical sample from a HPV-positive woman has been examined after 90 days, one reminder to book an appointment at the GP will be sent by digital mail.

If the self-sample is HPV negative, follow-up will be conducted according to age and screening history. HPV-negative women aged 50-59 years will be referred back to the national screening

programme. Women aged 60-64 years who have a normal cervical sample within the past six years will exit the screening programme. Women aged 60-64 years without a normal cervical sample within the past six years will be re-invited within 12 months to do an additional self-sample for HPV before they exit the programme. This is according to new guidelines on HPV self-sampling in Denmark for women aged 60-64 years [21]. If the self-sample is invalid, the woman will be advised to see her GP for a cervical sample.

If the woman returns a self-collected FIT, she will receive the result by digital mail and the GP will also receive the result within two weeks from returning the completed sample. Follow-up is conducted according to the national screening programme [22]. Thus, if the FIT is positive for traces of blood, the woman will be contacted by surface mail with a pre-booked appointment for colonoscopy within 14 days at a hospital-based screening endoscopy unit. If the woman does not show up for the colonoscopy, she will be reminded twice by digital mail and once by telephone with advice to book a new appointment. If the FIT is negative, the woman will be referred back to the national screening programme through a new invitation sent out two years later. If the test is invalid, a new test kit is sent to the woman.

Since the study is nested within national cancer screening programmes, the clinical management strategies used in the study must adhere to national guidelines. If the current national guidelines are updated during the study period, details relating to the study may be changed accordingly, and the project leader will be responsible for passing on the information to relevant partners.

Outcomes

Main effect measures

1) Difference between the control and the intervention group in overall coverage of CCU (self-sample or cervical cytology sample) and/or CRC (FIT) screening six months after the visit in the breast cancer screening unit measured as the proportion of women adherent with CCU

and/or CRC screening for the past 3.5/5.5 years according to age for CCU screening and the past two years and 4.5 months for CRC screening.

2) Difference between the control and the intervention group with respect to CCU (self-sample or cervical cytology sample) and/or CRC (FIT) screening participation six months after the intervention for the women who are overdue for CCU/CRC screening at the intervention date.

Secondary outcomes

Among the women who are overdue for CCU screening, the secondary outcomes will be prevalence of HPV in vaginal self-samples, compliance with follow-up in HPV-positive women (timely follow-up will be reported as a GP-collected cervical sample within 180 days from the HPV-positive sample), screening history of self-samplers ("under-screened" defined as screened at least once with a cytology sample within the ten years leading up to the inclusion date, but not screened within the past five years and six months, "un-screened" defined as no cytology sample registered within the past ten years), referral rate for colposcopy, incidence of cervical intraepithelial neoplasia of grade 2+ (CIN2+) (including CIN2, CIN3/adenocarcinoma in situ (AIS) and carcinoma), incidence of HPV-positive cases in women 60-64 years after 12 months with an initial negative HPV sample.

For those who are overdue for CRC screening, secondary outcomes will be prevalence of positive FIT cases, compliance with follow-up (timely follow-up will be reported as colonoscopy within 60 days from a positive FIT), screening history of women who receive a new FIT ("under-screened" defined as a minimum of one FIT, but no FIT within the past two years and 4.5 months, "un-screened" defined as no previous FIT despite invitation) histology (adenomas and cancer).

Participation after subsequent screening invitation in all three cancer screening programmes five years after the intervention may be measured.

Process outcomes

In the intervention group, process outcomes will be the proportion of women accepting a check-up on their CCU and CRC screening status, the proportion of women overdue for CCU and/or CRC screening, the proportion of women accepting a test-kit and the proportion of women not returning the kit.

The surveys sent to the women after inclusion will be used to evaluate the acceptability of the intervention and the participants' satisfaction with the breast cancer screening.

Other variables

Outcomes to test if the randomisation succeeded will be screening history, previous cancer diagnoses, hysterectomy, inflammatory bowel disease (IBD) and socioeconomic data (age, ethnicity, marital status and educational level).

Sample size

Preliminary data from a study of the proportion of women participating in one, two or all three Danish cancer screening programmes show that approximately 20% of women participating in breast cancer screening did not participate in CCU screening (excluding women with hysterectomy or a Charlson comorbidity score ≥ 3), and approximately 35% did not participate in CRC screening (excluding women with a previous diagnosis of colorectal cancer or a Charlson comorbidity score ≥ 3) (unpublished data).

The premise is to attend each breast cancer screening unit 20 times, corresponding to a total of 100 intervention days. Every unit has pre-booked approximately 74 women daily of whom 55 are expected to attend. Assuming that 40 women per day are eligible for CCU screening and 52 for CRC screening, leaving a study population of 4000 and 5200 women respectively, the study may detect a difference in screening coverage as low as 2.3% in CCU screening (increasing from 80% to 82.3%) and 2.4% in CRC screening (increasing from 65% to 67.4%) with a risk of type 1 error of 5% and type 2 error of 10% (power of 90%). In the analyses, women who have had hysterectomies and/or CCU/CRC will be excluded.

A design effect due to cluster randomisation is not taken into account as the intervention will be equally distributed between the screening units over the entire study period. The individuals within the clusters are considered independent of each other [23].

Enrolment was initiated in September 2021 and is expected to go on for one year.

Data sources

The study population will be identified in the regional administrative system of the breast cancer screening programme. On intervention days, the current status of participation in CCU screening will be obtained from the Danish Pathology Register (DPR), which holds data on cervical cytology samples in Denmark [24]. Furthermore, the current status of participation in CRC screening will be obtained from the Invitation and Administration Module (IAM), which holds data on FIT in Denmark.

Data on test results from cytology, HPV test, colposcopies and screening history in CCU screening will be retrieved from the DPR and the Danish CCU Screening Database [25]. Data on screening history in CRC screening and data on FIT result, colonoscopies and histology will be retrieved from the Danish CRC Screening Database [26].

Furthermore, data on previous cancer diagnoses will be drawn from The Danish Cancer Registry [27] and The Danish National Patient Register [28] which will also provide data on IBD and total hysterectomies (codes are provided in Table 1) [29].

Table 1 International Classification of Diseases (ICD) codes used to identify previous cancer diagnoses, total hysterectomies and irritable bowel disease

	ICD-7/8	**ICD-10**
Colorectal cancer	153.x, 154.x, 253.x, 453.x, 454.x, 653.x, 654.x, 753.x, 754.x, 853.x, 854.x;	C18-20
Cervical cancer	171.x, 671.x, 771.x, 871.x;	C53
Hysterectomy	ICD-8 (1977-1995) surgical procedure codes: opr61050, opr61020, opr72230, opr61040, opr72650, opr61100, opr72240, opr61780, opr62300	ICD-10 surgical procedure codes: KLCD00, KLCD01, KLCD04, KLCD10, KLCD11, KLCD30, KLCD31, KLCD40, KLCD96, KLCD97, KLDC10, KLDC13, KLDC96, KLDC20, KLDC23, KZXX00, KMCA33, KLEF13, KLEF00B
Irritable bowel disease		DK50-51

Note: Danish Cancer Register used ICD-7, Danish National Patient Register used ICD-8.

Statistics Denmark will provide sociodemographic data [30]. Using Statistics Denmark's classification, ethnicity will be categorised by country of origin as either Danish, Western (EU, Andorra, Australia, Canada, Iceland, Liechtenstein, Monaco, New Zealand, Norway, San Marino, Switzerland and the USA) or non-Western (others). Marital status will be classified as cohabitating or living alone. Highest educational attainment will be classified according to UNESCO's classification as low (≤ 10 years), middle (11–15 years) or higher education (> 15 years).

The study cohort will be managed in REDCap, which is a secure web application for building and managing online surveys and databases [31]. All data will be linked at the individual level using the unique ten-digit CPR number assigned in Denmark at birth or upon emigration [26].

Statistical analyses

Baseline characteristics in both groups will be presented using descriptive statistics (number and proportions) to determine if the randomisation was equally balanced.

Differences in coverage and participation rates between the intervention and the control group will be estimated both as absolute difference and relative risk with 95% confidence intervals (CIs).

Secondary and process outcomes will be reported by descriptive statistics including 95% CIs.

All statistical analyses will be conducted using STATA V. 16.

In case shewed selection is detected due to cluster randomization, adjusted analyses will be performed for relevant confounders.

Patient and public involvement

The study design was pilot tested for feasibility and acceptability, the latter including women attending the breast cancer screening unit at the days of pilot testing. These women were asked to share their experience with the intervention. The responses were analysed to ensure participant satisfaction with the intervention. Other than this, neither patients nor the public will be involved in this research. We plan to disseminate the results to the general screening population and patient organisations through mass media.

ETHICS AND DISSEMINATION

According to the EU's General Data Protection Regulation (Article 30), this project is listed in the record of processing activities for research projects in the Central Denmark Region (R. No.: 1-16-02-217-21). Under the Consolidation Act on Research Ethics Review of Health Research

Projects, Consolidation Act number 1083 of 15 September 2017, Section 14 (2), notification of medical database research projects to the research ethics committee system is required only if the project involves human biological material. Thus, this study was not notifiable to the Committee (R. No.: 1-10-72-1-21). Accordingly, information may be retrieved from regional administrative systems and registers without informed consent from the participants when approved by the hospital management. The hospital management at Randers Regional Hospital, Central Denmark Region, has approved this project. The study is registered with clinicaltrials.gov (R. No. NCT05022511) (see Table 2 for the World Health Organization Trial Registration Data Set) and will be conducted in accordance with the Good Clinical Practice Guidelines.

The results will be reported in international peer-reviewed scientific journals and compiled as a thesis, which will be submitted for examination for a PhD at Aarhus University, Denmark. Furthermore, results will be presented at national and international scientific meetings and disseminated to healthcare stakeholders, patient organisations and the general public through press releases.

Table 2 All items from the World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT05022511
Date of registration in primary registry	10 August, 2021
Secondary identifying numbers	N/A
Source(s) of monetary or material support	The University Research Clinic in Cancer Screening and the Department of Public Health Programmes, Randers Regional Hospital, Denmark
Primary sponsor	The Department of Public Health Programmes and the University Clinic in Cancer Screening, Randers Regional Hospital, Denmark
Secondary sponsor(s)	Department of Clinical Medicine, Aarhus University, Denmark
Contact for public queries	Anne Dorte Lerche Helgestad, MD [annesper@rm.dk]
Contact for scientific queries	Anne Dorte Lerche Helgestad, MD Department of Public Health Programmes and University Clinic in Cancer Screening, Randers Regional Hospital, Denmark
Public title	Three birds with one stone
Scientific title	Three birds with one stone: a randomised intervention study to increase participation in cervical and colorectal cancer screening among women attending breast cancer screening
Countries of recruitment	Denmark

Data category	Information
Health condition(s) or problem(s) studied	Cervical cancer and colorectal cancer screening
Intervention(s)	Active comparator: An offer to receive information on screening status in cervical and colorectal cancer screening when attending breast cancer screening. If overdue for one or both screening programmes, self-sampling screening test(s) is/are offered.
	Control comparator: Standard screening offers according to the national screening programmes
Key inclusion and exclusion criteria	Ages eligible for study: 50-64 years (cervical cancer screening), 50-69 years (colorectal cancer screening) Sexes eligible for study: women Accepts healthy volunteers: no
	Inclusion criteria: women aged 50-69 years booked for a breast cancer screening on an intervention day
	Exclusion criteria: Not eligible for cervical or colorectal cancer screening, did not attend breast cancer screening, changed appointment for breast cancer screening after randomisation, insufficient Danish skills to provide informed consent
Study type	Interventional
	Allocation: cluster randomised intervention model. Parallel assignment 1:4.
	Primary purpose: prevention
Date of first enrollment	September 2021
Target sample size	37,000
Recruitment status	Recruiting
Primary outcome(s)	1) Difference between intervention and control group with respect to coverage in cervical cancer/colorectal cancer screening six months after the intervention. 2) Difference between the intervention and the control group in proportion of women participating in cervical cancer and colorectal screening after six months for women who were overdue for their cervical cancer/colorectal cancer screening at the intervention.
Key secondary outcomes	For both cervical and colorectal cancer screening, secondary outcomes will be screening-related outcome, clinical follow-up, satisfaction with breast cancer screening during intervention and process outcomes.

PERSPECTIVES

To our knowledge, this study will be the first of its kind to offer an inter-programme collaboration between three cancer screening programmes simultaneously by reaching out to women overdue for CRC and/or CCU screening when participating in breast cancer screening. By reducing logistic challenges and taking advantage of a more personalised communication with the women, this study may enhance participation in un- and under-screened women who have not deliberately chosen not to participate. These women are presumably susceptible to

preventive healthcare but for a host of reasons end up as non-participants. Women who do not participate in breast cancer screening must be targeted by other interventions.

A strength of this study is that it is an easily scalable intervention, which - in case of a positive result – has the potential to be implemented in the national screening programme at the breast cancer screening units without great costs.

Contributorship statement

ADLH is the principal investigator of the study and responsible for the coordination of the trial with supervision from MBL and BA. ADLH, MBL and BA are primarily responsible for the study design with input from SN, MT and LKP.

MT and LKP contributed advice and knowledge on CCU screening, follow-up after CCU screening and self-sampling. SN contributed advice and knowledge on CRC screening, follow-up after CRC screening and statistical considerations.

ADLH drafted the manuscript. All authors contributed with further development of the manuscript and reviewed and approved the final version.

Competing interests

Roche Diagnostics sponsors the Cobas 4800 HPV DNA tests. According to the contract between Roche Diagnostics and the University Research Clinic for Cancer screening, the Department of Public Health Programmes, Randers Regional Hospital, Roche Diagnostics has no influence on the scientific process and no editorial rights pertaining to this manuscript. MT, LKP and BA have participated in other studies with HPV DNA tests sponsored by Roche Diagnostics. MT has received honoraria from Roche Diagnostics for lectures on HPV self-sampling. SN has received a speaking fee from Norgine and LKP has received speakers fee from Astra Zeneca and MSD.

Data availability statement

Under Danish law, restrictions will apply to the availability of the data generated during this study. Register data will be used under a license for the present study and may be available

upon reasonable request to the Danish Health Data Authority and Statistics Denmark. The participants will not be asked to provide consent for publication of the questionnaire data, but data may be available in anonymous form from the corresponding author upon reasonable request.

Funding

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Protocol version

Issue date: 11 March 2022, version 1

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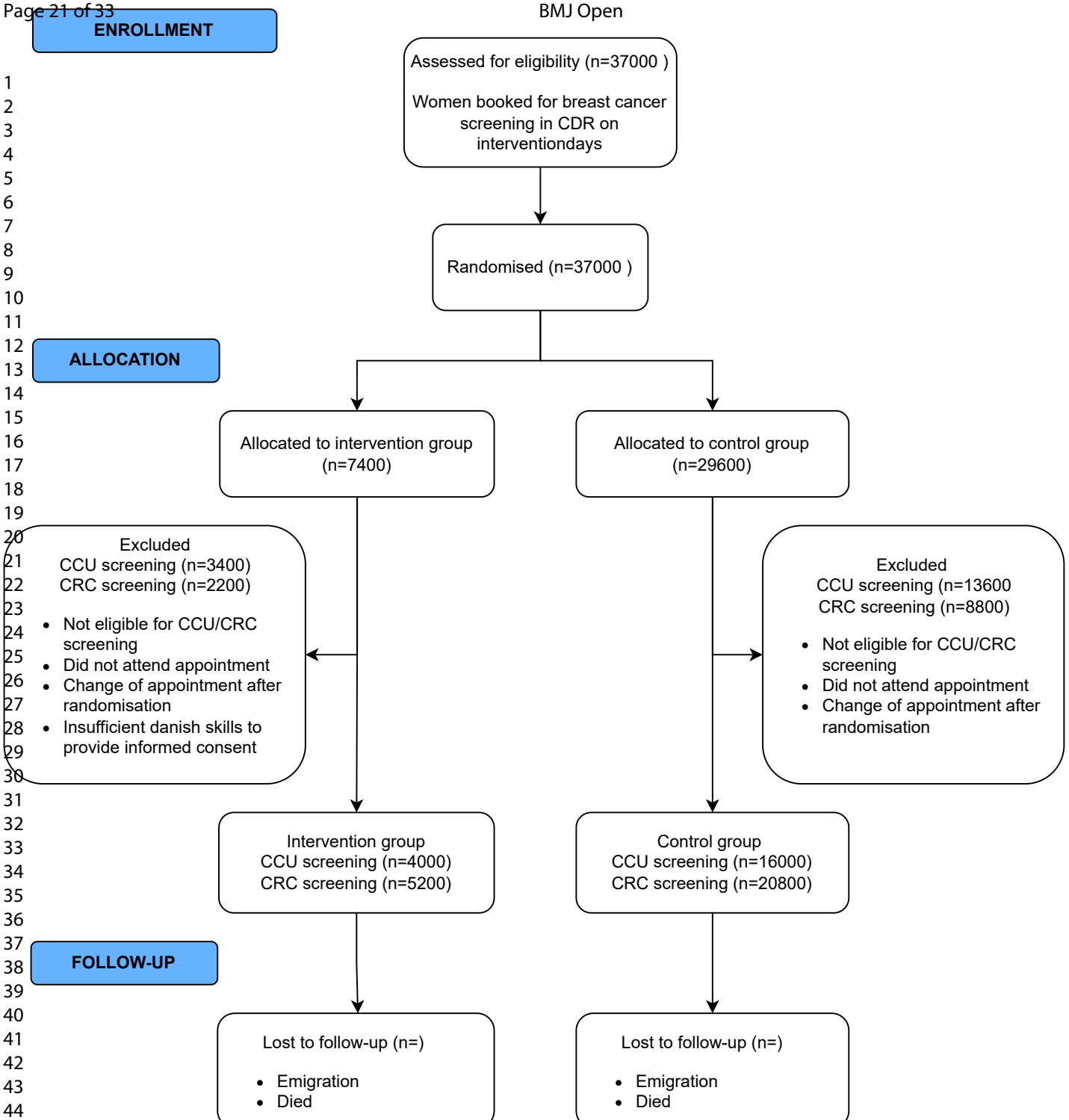
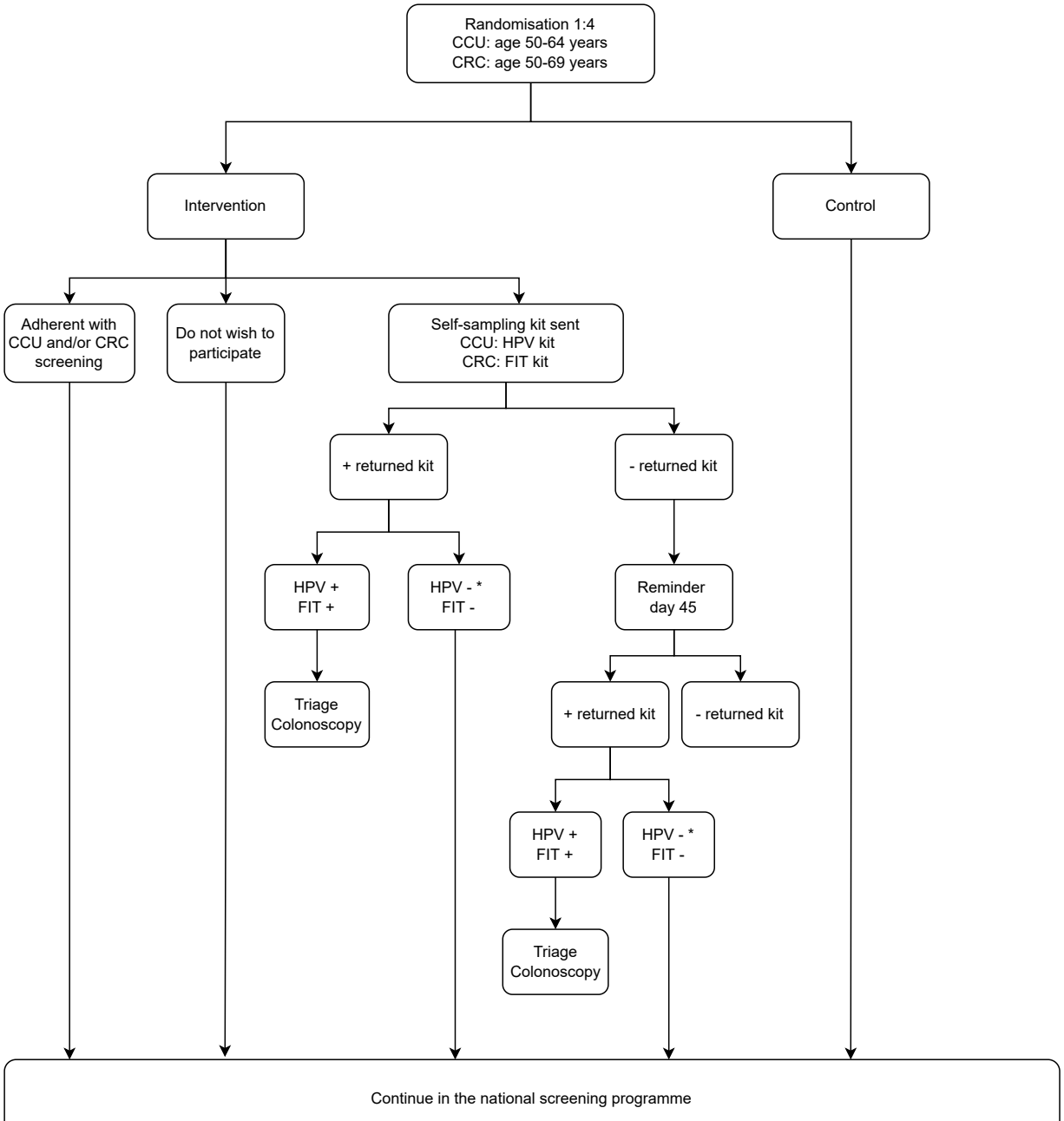
Figure 1 CONSORT 2010 flow diagram of the study

Figure 2 Flow diagram of the intervention





*Women aged 60-64 years will receive a new self-sampling kit in one year according to current Danish guidelines.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15, table 2
Protocol version	#3	Date and version identifier	18
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16, 17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	N/A

		management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9, figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods:			
Assignment of			

interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A No blinding

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to	12,15

		promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A The trial is with minimal risks and of short duration; hence it has been decided that there will be no need for a DMC

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A No interim analysis will be made.
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8, 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14, 17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A