Submitted to the Social Security and Health Chamber of the Belgian Information Security Committee on 17/01/2025 (Deliberation VC/KSZG/25/094 of 16/04/2025).

# STUDY PROTOCOL
# SOCIAL SCIENCES AND HUMANITIES STUDY

## *Equity in breast cancer screening in Flanders: the necessity of tailored reminders for women with low socioeconomic status*

| | |
|---|---|
| **Reference number STK** | CPR-2022/1888 |
| **Acronym** | **ENTER** (Equity iN breasT cancEr scReening) |
| **Principal Investigator** | Guido Van Hal |
| **Co-investigators** | Allegra Ferrari, Lilu Ding, Wessel van de Veerdonk, Sarah Talboom, Liesbet Van Bos, Mathieu Goossens |
| **Research title** | Equity in breast cancer screening in Flanders: the necessity of tailored reminders for women with low socioeconomic status |
| **Project duration** | 24 months |
| **Ethical clearance** | Approved by UA Ethics Committee with final decision on 7/12/23 (Ref: EX_SHW_2023_40_1) |
| **Abstract** | The Flemish Breast Cancer Screening Program (BCSP) has been implemented in 2001, only 50% of eligible women were screened on average from 2016 to 2020. Moreover, women of low socioeconomic status (SES) were 40% less likely to participate in the BCSP than women of high SES. In addition, the chances of participation upon receival of a new invitation are only about 10% in previous non-responders. To improve the equity of BCSP participation in Flanders, interventions to tackle barriers and misconceptions towards BCSP for low-SES non-participants are needed. While a normal reminder regarding time and place of screening can improve participation in randomized controlled trials, participation in some countries that applied reminders in BCSP remains modest. The BCSP in Flanders has not introduced reminders also because of the lack of evidence of the cost- effectiveness of the reminders. For this project, a reminder tailored for low-SES women who failed to respond to their latest invitation was developed in co-creation with target audience as well as domain experts. The effectiveness of the intervention will be tested in a RCT with the support of the CvKO.<br>The cost-effectiveness of the interventions will beevaluated with a validated micro-simulation model. |

## Project team and affiliations

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**Social Epidemiology and Health Policy (SEHPO), UAntwerpen**
The Social Epidemiology and Health Policy (SEHPO) research group aims to conduct research in the areas of social epidemiology, environmental epidemiology and preventive health care with a focus on policy support. The interdisciplinary nature of SEHPO allows us to provide valuable insights into societal health issues and evidence-based policy support.
For example, staff at SEHPO have expertise in conducting large-scale observational studies, evaluating cancer screening programs, and investigating environmental epidemiological issues. Within SEHPO, this expertise is combined to apply research to a wide range of populations (e.g., children, students, older adults, vulnerable or marginalized groups etc.). In terms of health policy, much research is conducted within SEHPO on cancer screening, as mentioned above. These include breast, cervical, colon and lung cancer screening. Staff from SEHPO also regularly conduct policy support research on demand for the Superior Health Council.

**Thomas More**
The 120 researchers and consultants of the Research & Innovation Unit of Thomas More conduct practice- oriented research and aim to bridge the gap between research and practice. By transferring scientific evidence and knowledge into tangible and practical solutions or advice they create real societal and/or economic impact. Research activities often have a multidisciplinary approach and are carried out in close cooperation with several partners. The R&I Unit has a proven track record in (inter)national funded research and innovation projects. Within the research domain

Health & Care Challenges, the project will be carried out by dr. Wessel van deVeerdonk, together with the expert group Strategic and Effective Communication drs. Sarah Talboom.

**CVKO**

The Centre for Cancer Detection (CvKO) is the expert centre for population screening for cancer in Flanders. They monitor international developments and conduct scientific research. For this, they can rely on the knowledge, expertise and experience of a team of scientists, doctors and administrative and technical staff. Every year, the CvKO invites 1.5 million people in Flanders per postal invitation to undergo preventive screening for breast cancer, colorectal cancer or cervical cancer. In order to properly inform the target groups and by extension the entire population, the CvKO work closely with partners in the health care sector such as general practitioners, gynaecologists, gastroenterologists, radiologists, the Flemish Logos, mutual health organisations and the Institute for Healthy Living.

## Description of the research project

The "ENTER" project is funded by the Foundation against Cancer (StK) and implemented by the University of Antwerp (UA), with the support of Thomas More and CvKO. The project has been approved by the UA Ethics Committee (7/12/23) and the Vlaamse werkgroep Bevolkingsonderzoek Borstkanker (22/01/24).

### Background

Breast cancer (BC) mammography screening can reduce BC mortality by up to 40%. In order to get the maximum benefit of mortality reduction of a Breast Cancer Screening Program (BCSP), it is important to involve as many (well-informed) eligible women for screening as possible. While the BCSP has been implemented in Flanders since 2001, only 50% of eligible women on average were screened every year. Moreover, participation inequity was observed, where women with low socioeconomic status (SES) were up to 40% less likely to participate in the BCSP than high-SES women. In addition, it is estimated that the chances of participation upon receival of a new invitation are only about 10% in previous non-responders. Tailored interventions based on a systematic understanding of the barriers and misconceptions towards BCSP are needed especially for low-SES non-participants in order to improve the equity of the BCSP.
In order to improve participation in BCSPs, normal reminders regarding screening time and place have been implemented widely based on the proven effect of participation improvement of non-responders by up to 90% in randomized controlled trials (RCTs). However, only a 50% participation rate was achieved in some countries that applied reminders. The gap in the effect of reminders between the RCTs and the BCSPs indicates an opportunity to engage more vulnerable or marginalized women in the BCSP. Up till now, the BCSP in Flanders has not applied any reminder due to a lack of evidence regarding the (cost-effectiveness) of this intervention. Therefore, the primary objective was to develop a reminder about the BCSP targeted for the low-SES group and to evaluate its effectiveness and cost-effectiveness.

### Objective

The objective of this study is to test whether a personalized reminder letter can increase the response rate to the BCSP among “non-attender” women with low socioeconomic status (SES).

## Study design

The effectiveness of the reminder letter will be tested in a two-arm, non-blinded randomized controlled trial (RCT).

Participants will be divided in to two groups, with a randomization 1:1 at the mammographic unit level. This means that, instead of randomizing the entire population on a 1:1 basis (where half of the participants would be assigned to one group and half to the other), the randomization will be done separately within each mammographic unit. In other words, for every mammographic unit, the invited participants will be randomly divided into two groups in a 1:1 ratio.
The intervention group (Group A) will receive by mail the tailored reminder letter (1 week before the screening date, with a variation of 2-4 days) in addition to the regular invitation letter to the BCSP program (received 3 weeks before the screening date, with a variation of 2-4 days).

The control group (Group B) will not receive a reminder.

The outcome will be measured as response rate in the BCSP <40 days after the invitation is sent, in total and stratified by SES (after linkage of participation data with socioeconomic data).

## Study population

The study population consists of previously "non-attender" women in the BCSP invited to a selected list of 67 mammographic units located in municipalities in Flanders that were considered "low-SES", during the months of April, May and June 2024.

In the Flemish BCSP, organized, coordinated, and monitored by the Centre for Cancer Detection (CvKO), women aged 50–69 can are invited to receive a screening mammography every other calendar year.
A "non-attender" (type 4) is a person that, at the time of the current planning, (i) have had at least one previous invitation and (ii) have never participated in the past. These women are scheduled for an appointment in a screening unit near their home.
Mammographic units were selected from the low-SES municipalities in Flanders. Municipalities with low-SES scores were defined by at least two of the following: (i) average income per capita <20.000 EUR; (ii) Belgian Multiple Index of Deprivation <6; (ii) increased reimbursement >12% (https://provincies.incijfers.be/databank; https://bimd.sciensano.be/tool).
Because the intervention is targeted for a low-SES group, a linkage of individual participation status to individual socioeconomic data will be requested to the InterMutualistisch Agentschap (IMA) after completion of the RCT.
After linkage, the IMA will provide aggregated data of mean participation by SES group. The "SES group" variable will created based on a set of variables (minimum 2, maximum 4) agreed with IMA. Approval from the Informatieveiligheidscomité (IVC) will be requested for this linkage.

## Power calculation

The estimated response in previous non-attenders in Flanders is 10% (Goossens et. Al 2023). Considering an expected absolute increase of 5% in the intervention group in comparison with the control group (Allgood et al. 2016), with alfa 0.05 and beta 0.80, the estimated sample is 686 per arm, for a total of 1372. Because the expected share of people with low-SES in the selected municipalities is 20% (https://provincies.incijfers.be/databank), the sample size will be increased by 5 times to 3430 per arm, for a total of 6860.

## Statistical analysis

The difference in attendance between control and intervention arm will be compared with Chi square test for the primary endpoint. Results will be reported as ORs with 95% confidence intervals (CIs) for participation.

**Control:** Regular invitation letter

**Intervention:** Regular invitation letter + tailored reminder

The reminder contains simple, tailored information, graphically and linguistically adapted for a low-literate audience. Besides the time and place for screening, the reminder contains a QR code to download the reminder in several languages (Arabic, Albanian, Dutch, English, Farsi, French, German, Italian, Romanian, Russian, Spanish, Turkish).

- Development

First, three focus group discussions (FGDs) including a sample of 19 low-SES women living in Flanders (16 immigrant and 3 Flemish women) were conducted by UA and Thomas More between April and June 2023. The most commonly reported barriers and facilitators for participation as well as words and expression more easy or difficult to understand in the official invitation letter were used to draft the first version of the tailored reminder.

Secondly, on the base of the insights from the FGDs, the reminder was developed in co-creation with target audience as well as domain experts. In particular, a Delphi method was employed to establish consensus among a panel of 8-10 relevant stakeolders (including people and organizations working with low-SES women such as Solidaris, Logo, FMDO, AZ Damian, Saamo, Community Health Workers, the program manager of the BCSP in Flanders, and health and social workers). They were consulted in three rounds of consultations organized by UA and Thomas More. Finally, in collaboration with Saamo (Together Tackling Exclusion) and FMDO (Federation for Global and Democratic Organizations), Thomas More performed a co-creation session of the reminder with low-SES women to evaluate the understandability and other topics end-users brought up as important on the content developed by the experts. The co-creation session involved 14 low-SES participants (13 immigrant and 1 Flemish women). The final concept version of the reminder was sent to experts of the Delphi panel as a member check to finalize the tailored reminder.

- Planning

The study will include previous non-attenders invited to a selected list of 67 mammographic units located in municipalities in Flanders that were considered “low-SES”.

For each mammographic unit all previous “non-attenders” that are scheduled to receive an invitation in the study period (April-June 2024) will be selected for the study until the required sample size is reached (6860).

Based on the expected number of non-attenders that will receive an invitation during the study period (CVKO - Heracles planning) the RCT is expected to last 1-3 months. However, the period can be altered (shortened-prolonged) based on the actual number of invitations that are sent.

The randomization will be conducted at the mammographic unit level, with selected participants within mammographic unit allocated to either the intervention or control group in a 1:1 ratio. In other words, instead of randomizing the entire sample globally (6860 participants are divided into 3430 per arm) randomization will occur separately within each mammographic unit (https://borstkanker.bevolkingsonderzoek.be/nl/bk/overzicht-mammografische-eenheden).

In the screening program, most of the invitations are prepared for sending 5 weeks before the appointment date and sent via BPost on fridays, in order to to be received in the week thereafter, about 3-4 weeks before the appointment date.
For this study, given a certain appointment date (A) reminders will be prepared 14 days in advance (B) and sent via BPost 10 days in advance (C), in order to be received in the week thereafter, 1 weeks before the appointment date, with a variation of 2-4 days.

A) Appointment date
B) Date in which the invitation is made: 14 days before A
C) Date in which the invitation is sent: 10 days before A

**Data flow**

Following the completion of the study, a report of results including only numbers by category (not study identification numbers nor rijksregisternummer) will be provided to UAntwerpen by the CvKO.
To evaluate socio-economic status (SES)-related differences in response rates, UAntwerpen will submit a request to link participation data from the dataset of the ENTER study. In particular, a report including only numbers by category (not study identification numbers nor rijksregisternummer) will be requested to the InterMutualistisch Agentschap (IMA). The key to making this link is the rijksregisternummer of all women randomized in the ENTER study, which will be provided encrypted via a Third Trusted Party (TTP) upon reception of approval from the Informatieveiligheidscomité (IVC)

## Bibliography


Goossens MM, Kellen E, Broeders MJM, Vandemaele E, Jacobs B, Martens P. The effect of a pre-scheduled appointment on attendance in a population-based mammography screening programme. Eur J Public Health. 2023;33(6):1122-1127. doi:10.1093/eurpub/ckad137

Allgood PC, Maxwell AJ, Hudson S, et al. A randomised trial of the effect of postal reminders on attendance for breast screening. Br J Cancer. 2016;114(2):171-176. doi:10.1038/bjc.2015.451

Rosner B. Fundamentals of Biostatistics. 7th ed. Boston, MA: Brooks/Cole; 2011.

Flemish Provincial Authorities. Accessed online: https://provincies.incijfers.be/dashboard/dashboard/

InterMutualistisch Agentschap (IMA). Atlas. Accessed online: https://atlas.ima-aim.be/databanken/?rw=1&lang=nl

InterMutualistisch Agentschap (IMA). Verhoogde tegemoetkoming en vervangingsinkomen in België. Accessed online: https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fima-aim.be%2FVerhoogde-tegemoetkoming-en%3Flang%3Dnl%23%3A~%3Atext%3DIn%25202022%2520had%252020%2525%2520van%2

Ctot%2520de%2520gezondheidszorg%2520te%2520verbeteren&data=05%7C02%7CAllegra.Ferrari%40uantwerpen.be%7Cdf76a80b7aaf46faaa3308dc233afb3e%7C792e08fb2d544a8eaf72202548136ef6%7C0%7C0%7C638423983425584308%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C0%7C%7C%7C&sdata=lDQr8qO41Jra4uT3N3L%2Fy3Ps%2BTTXaZGQq9ngYqyBndI%3D&reserved=0

Approved by the EA SHW Ethics Committee of the University of Antwerp on 07/12/23.
(Ref. EX_SHW_2023_40_1)

University of Antwerp

Stichting tegen Kanker
Fondation contre le Cancer

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| **Research title** | Equity in breast cancer screening in Flanders: the necessity of tailored reminders for women with low socioeconomic status |
| **Abstract** | The Flemish Breast Cancer Screening Program (BCSP) has been implemented in 2001, only 50% of eligible women were screened on average from 2016 to 2020. Moreover, women of low socioeconomic status (SES) were 40% less likely to participate in the BCSP than women of high SES. Misconceptions towards BCSP are one of the most prominent reasonsfor the non-participation in BCSP. To improve the equity of BCSP participation in Flanders, interventions targeting to tackle misconceptions towards BCSP for low-SES non-participants are needed. While a normal reminder regarding time and place of screening can improve participation in randomized controlled trials, participation in some countries that applied reminders in BCSP remains modest. The BCSP in Flanders has not introduced reminders also because of the lack of evidence of the cost- effectiveness of the reminders. For this project, a reminder tailored to tackle the misconception towards BCSP will be developed. Low-SES women who failed to respond to their latest invitation will get the reminder by mail.<br>Knowledge, attitude towards BCSP, and participation in BCSP will be measured by a validated questionnaire before and after the reminder in a cross-over cohort study. The cost-effectiveness of the interventions will beevaluated with a validated micro-simulation model. |

## Project team and affiliations

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## 1. Introduction

| | |
|---|---|
| **Title of the research project** | Equity in breast cancer screening in Flanders: the necessity oftailored reminders for women with low socioeconomic status |

| **Abstract of the research project** |
|---|
| The Flemish Breast Cancer Screening Program (BCSP) has been implemented in 2001, only 50% of eligible women were screened on average from 2016 to 2020. Moreover, women of low socioeconomic status (SES) were 40% less likely to participate in the BCSP than women of high SES. Misconceptions towards BCSP are one of the most prominent reasons for the non-participation in BCSP. To improve the equity of BCSP participation in Flanders, interventions targeting to tackle misconceptions towards BCSP for low-SES non-participants are needed. While a normal reminder regarding time and place of screening can improve participation in randomized controlled trials, participation in some countries that applied reminders in BCSP remains modest. The BCSP in Flanders has not introduced reminders also because of the lack of evidence of the cost-effectiveness of the reminders. For this project, a reminder tailored to tackle the misconception towards BCSP will be developed. Low-SES women who failed to respond to their latest invitation will get the reminder by mail. Knowledge, attitude towards BCSP, and participation in BCSP will be measured by a validated questionnaire before and after the reminder in a cross-over cohort study. The cost-effectiveness of the interventions will be evaluated with a validated micro-simulation model. |

| **Project duration** |
|---|
| 24 months |

| | |
|---|---|
| **Research area based on theEuropean Code Against Cancer** | Focus on secondary prevention (screening strategies) |

## 2. Description of the research project

**Description**

Breast cancer (BC) mammography screening can reduce BC mortality by up to 40%. In order to get the maximum benefit of mortality reduction of a Breast Cancer Screening Program (BCSP), it is important to involve as many (well-informed) eligible women for screening as possible. While the BCSP has been implemented in Flanders since 2001, only 50% of eligible women on average were screened every year. Moreover, participation inequity was observed where women with low socioeconomic status (SES) were 40% less likely to participate in the BCSP than high-SES women. Studies have shown that misconceptions about BCSP are one of the most prominent reasons for non-participation, for example, the idea that screening is only necessary for old women, or women with a family history of BC, and that screening is dangerous. Therefore, tailored interventions based on a systematic understanding of the misconceptions towards BCSP are needed especially for low-SES non-participants in order to improve the equity of the BCSP.
In order to improve participation in BCSPs, normal reminders regarding screening time and place have been implemented widely based on the proven effect of participation improvement of non-responders by up to 90% in randomized controlled trials (RCTs). However, only a 50% participation rate was achieved in some countries that applied reminders. The gap in the effect of reminders between the RCTs and the BCSPs indicates the challenge to engage women who have misconceptions towards BCSP. They may not participate after a reminder due to the same misconceptions as the original invitation. Up till now, the BCSP in Flanders has not applied any reminder due to a lack of evidence regarding the (cost-)effectiveness of this intervention.

Therefore, our primary objective is to improve the participation of low-SES women in the BCSP by developing a tailored reminder that addresses their misconceptions about the BCSP. Second, we will evaluate the cost-effectiveness of the tailored reminder in order to implement it in the BCSP. The project will contain four work packages (WPs). All organizations involved have provided letters of intent.

**WP 1 Mapping the strategies to increase participation in the BCSP among low-SES women**

We will perform a systematic review by systematic searching, selecting, and summarizing studies from Medline, Biological Abstracts and Global Health (via Ovid), Web of Science, Scopus, Cochrane Library, and Google Scholar. Subsequently, we will organize focus group discussions (FGD) with low-SES women to further collect misconceptions that are not covered by the review and to validate the findings from the review for Flanders. To reach the saturation point of the themes of our topic, three FGDs each with 6-8 participants will be organized. Participants will be recruited through an organization working with the low-SES population (KRAS).

**WP 2 Design a tailored reminder regarding the BCSP for low-SES women**

Based on insights from WP1 about the strategies to increase participation in the BCSP among low-SES women and the prevailing misconceptions about the BCSP, a tailored reminder will be developed in co-creation with target audience as well as domain experts. The reminder will include the time and place for screening combined with tailored information, aimed at tackling the misconceptions about the BCSP. The tailored reminder will be developed through a Delphi method to establish consensus. A panel of 8-10 participants from organizations working with low-SES women (Solidaris, Logo, FMDO, AZ Damian, Saamo, Community Health Workers...), the program manager of the BCSP in Flanders, and health and social workers will be consulted in three rounds of consultations organized by UA and Thomas More. Thomas More will perform a co-creation session of the reminder with low-SES women to evaluate the understandability and other topics end-users bring up as important of the content developed by the experts. Moreover, we will send the final concept version of the reminder to experts of the Delphi panel as a member check to finalize the tailored reminder.

**WP 3 Evaluate the effect of the tailored reminder on improving participation in the BCSP**

The developed reminder will be sent out to women from the target group in two quasi-experimental studies:

- At sector level, targeting women living in sectors below the Belgium poverty line at the lowest SES-scores (https://provincies.incijfers.be/databank). Based on sample size calculation, 1470 women per arm will be included in the study.
- At individual level, targeting low-SES women reached through people and organizations working in deprived areas. Additional 100 women per each arm will be included in the study.

In both studies, participants will be divided in to two groups (randomization 1:1). The intervention group (Group A) will receive, in addition to the regular invitation letter to the BCSP program, the tailored reminder developed by mail two weeks before screening.
Initially, the control group (Group B) will not receive any additional reminder. However, in order to take into account our responsibility to all participants, to provide the best and most effective services possible, after the effectiveness of the intervention has been evaluated (follow-up at 92 days), individuals in the control group that have not yet participated in screening, will also receive a reminder letter.

At sector level, the outcome will be evaluated as response rate <92 days following the mammography appointment.
At individual level, outcomes will include response rate <92 days following the mammography appointment and attitudes and beliefs towards the BCSP, evaluated by means of Champion's Health Belief Model Scale (CHBMS) and the Breast Cancer Awareness Measurement (BCAM) scale.

To this aim, participants in the study at the individual level will be asked to fill in a self-administered questionnaire twice, at enrollment, and two weeks after screening by means of a follow-up call. During this call, the research team will collect women's answers to the questionnaire and elaborate briefly on their reasons for participation/non-participation. They will also be asked about their intentions to participate in the future.

Sample size calculation:
The median 40-days response rate in sectors with average income below Belgium poverty line (€15,513/year) line is 37%. Because this is the median response rate in sectors where both low-SES and high-SES women may live, the calculation of the expected response rate in the control group was based on data from the InterMutualistisch Agentschap (IMA) data reporting a 6% lower participation rate among women with an increased reimbursement rate (RVT). With an expected response rate in the control group of 35%, an expected effect size of 5%, alpha 0.05 and beta 80%, at least 1470 women per arm are required for sufficient statistical power.

**WP 4 Evaluate the cost-effectiveness of the tailored reminders**
A micro-simulation model will be applied to estimate the effect of participation improvement in the BCSP on life- years gained (LYG), which cannot be observed in studies with limited follow-up time. The simulation model was originally developed for the Dutch BCSP and reported extensively in the literature. Briefly, the model will first be attuned based on the input parameters derived from women in Flanders then validated by a comparison between the model estimated number of screen-detected and interval BCs and the observed data in Flanders. With the validated model, scenarios with different participation rates due to the effect of reminders will be modeled resulting in an overview of LYG, and the cost-effectiveness when incorporating the additional cost due to sending out reminders will be estimated.

| **Project duration** |
| --- |
| 24 months |

## 3. Feasibility of the project

| **Scientific hypothesis** |
| --- |
| In Flanders, reminders have not been implemented in the general BCSP, let alone in the group of low SES. According to the published data from RCTs, the normal reminders regarding screening time and place can improve the participation rate of non-participants by 15%-90%. In this project, we will develop a tailored reminder that takes the prevailing misconceptions about the BCSP into account, we expect to see a larger improvement of participation rate of the non-participants. Therefore, the hypothesis for this study is that after the implementation of a reminder, tailored to the misconceptions towards BCSP, the participation rate in women with low-SES and the equity of the BCSP in Flanders will be improved. Moreover, the (cost-) effectiveness of a BCSP on life-years gained and BC mortality reduction in this group will be mapped and improved. |

| Objectives |
|---|
| The primary objective of this project is to improve the participation in BCSP by at least 5% for the low-SES non-participants included in the project.<br>The secondary objective is to evaluate the cost-effectiveness of the tailored reminder in the BCSP in women with low SES in Flanders. |

**Actions to achieve objectives**

| Start date | End Date | Tasks |
|---|---|---|
| 2022-11-1 | 2023-4-30 | 1. Perform a systematic review of interventions to increase participation in breast cancer screening.<br>2. Organize FGDs to validate and modify the misconceptions towards BCSP found in the systematic review. |
| 2023-5-1 | 2023-11-30 | 1. Design tailored reminders for women with low SES in a three-round Delphi consultation based on the data collected from the systematic review and the FGDs.<br>2. Customization and refinement of the tailored reminder with the active participation of women with low SES during a co-creative session. |
| 2023-12-1 | 2024-6-30 | 1. Select low-SES neighborhoods and organize meetings for the collection of informed consent, self-administrated questionnaire, and contact details.<br>2. Send the tailored reminder by mail to women in the intervention groups at both sector and individual level<br>3. Evaluate the effectiveness on the tailored reminder in improving participation and other outcomes such as knowledge and attitudes towards the BCSP. |
| 2024-7-1 | 2024-10-30 | 1. Evaluate the cost-effectiveness of the tailored reminder in the BCSP in Flanders.<br>2. Prepare manuscripts, conference presentations, and report of the project. |

**Risk analysis and risk management strategy**

The main risk is the potential low response of the targeted women in the baseline and the follow-up study. In order to include the required sample size, the following measures will be taken:

1) Active involvement of KRAS which is the field collaborator in this project. A letter of intent has been obtained from the collaborator. Furthermore, the informed consent, baseline questionnaires, and telephone numbers will be collected in a meeting organized by the KRAS which has a close connection with the low SES women. The follow-up will only be performed via a telephone call, without letting women travel, in order to minimize the dropouts.
2) During the development of the reminders, opinions will be collected from the target women to increase the understandability of the reminders to women. A member check will be performed by returning the final concept version of the reminder to experts in the Delphi group to further improve the tailored reminder.
3) Oversampling will be applied to account for the potential dropouts. Moreover, small presents like goody bags and multilingual reminders will also be applied depending on the language preference of the included women.

**In scope or out scope of the project**
Which actions & deliverables are included and excluded.

The **first** action is to systematically identify, describe, and appraise existing literature on interventions to increase participation in the breast cancer screening among females in the target age groups and evaluate the effectiveness/performance, where possible, performing a meta-analysis of quantitative results. To further suggest potential avenues for breast cancer screening intervention, a qualitative appraisal aimed at understanding knowledge gaps concerning interventions to increase cancer screening, with a focus on interventions conducted in different settings and populations (eg. age groups, socioeconomic status, nationality.. ), will be conducted. Results will be reported as a systematic review manuscript respecting the PRISMA guideline. In addition, a report of the FGDs regarding the misconception of low-SES women towards BCSP in Flanders willalso be delivered. The **second action** is to develop a tailored reminder for non-participants to tackle the misconception towards BCSP via a Delphi approach. The relevant deliverable will be the tailored reminder and a report of the Delphiconsultation process. The **third** action is to evaluate the effectiveness of the tailored reminder in two quasi-experimental studies and the cost-effectiveness of the tailored reminder in a micro-simulation modeling study. The relevant deliverable will be a report regarding the effectiveness and cost-effectiveness of the tailored reminder. The **last** action and the relevant deliverable is to develop and report an implementation plan for the tailored reminder. When positive results are obtained the intervention can be implemented broadly.

**Target Group**

Our project will focus on the low-SES women in order to improve the equity of participation in BCSP in Flanders.

Specifically, women aged 50-69 who live in neighborhoods that have an average income level in the lowest quartile of the national average income, meet our inclusion criteria. The sample size of our project, as calculated in the description of the application details, is 365 women, with the expected effect size, statistic power, and the potential dropouts considered.

**Informed consent procedure**

Verbal Informed Consent for women reached in the Individual level study

The PI retains overall responsibility for the informed consent of participants and will ensure that any person delegated to participate in the informed consent process is duly authorized, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice and the most recent version of the Declaration of Helsinki.

Because of the reasons described below, the study will be conducted based on prior verbal informed consents only.

Certain vulnerable populations may not be comfortable with signing written materials [Krousel-Wood et al., 2006]. Furthermore, we need to modify the informed consent in order to increase health literacy when working with vulnerable groups [Siegl, 2019; Tamariz et al.,2013].

For these reasons, simplified versions (including all the required components) of information form and ICF will be provided, as the language normally used in these documents is mostly incomprehensible for the target group population. Prior studies by Thomas More with vulnerable people have proven this: using an informed consent and the need to sign it had an impact on the study and the participants.

Signing the ICFs will cause distrust from the start of the study, even after participants are given a comprehensive but simple explanation. People want to participate, however signing a document represents a step too far. Especially for participants with limited reading and writing skills. Making these people sign the ICF would increase the barrier for vulnerable participants to take part in the research and increases inequity.

With a vulnerable population as defined, we can expect that only a limited amount of their time can be spent in a study (this is sometimes maximum a hour).

Therefore, especially if it is as interactive as our study is, a very efficient preparation and execution is needed. Explaining the study to people in easy language already takes some time. When it comes to signing this wakes a lot of distrust (e.g. one is talkative before asked to sign and silent afterwards; one really wants to participate but does not want to sign). Starting a study this way is not recommended and requires verbal consent to tackle.

For other recent study we were involved in, for the benefit of the participant as well as for the feasibility of the research, ethical committees of the University of Antwerp approved verbal consent for this population (*Ethics Committee for the Social Sciences and Humanities of the University of Antwerp under reference: SHW_21_77*; *Medical Ethical Committee UAntwerp / UZA - Project ID 3590- BUN B300202200010)*

ICFs will be provided to participants before the start of the study. As stated above, to limit lack of clarity for the population a simplified version will be provided so the participants have a better chance of understanding the study and it purpose before one decides about participation. In addition, the participants will have the possibility to ask questions to members of the research team.

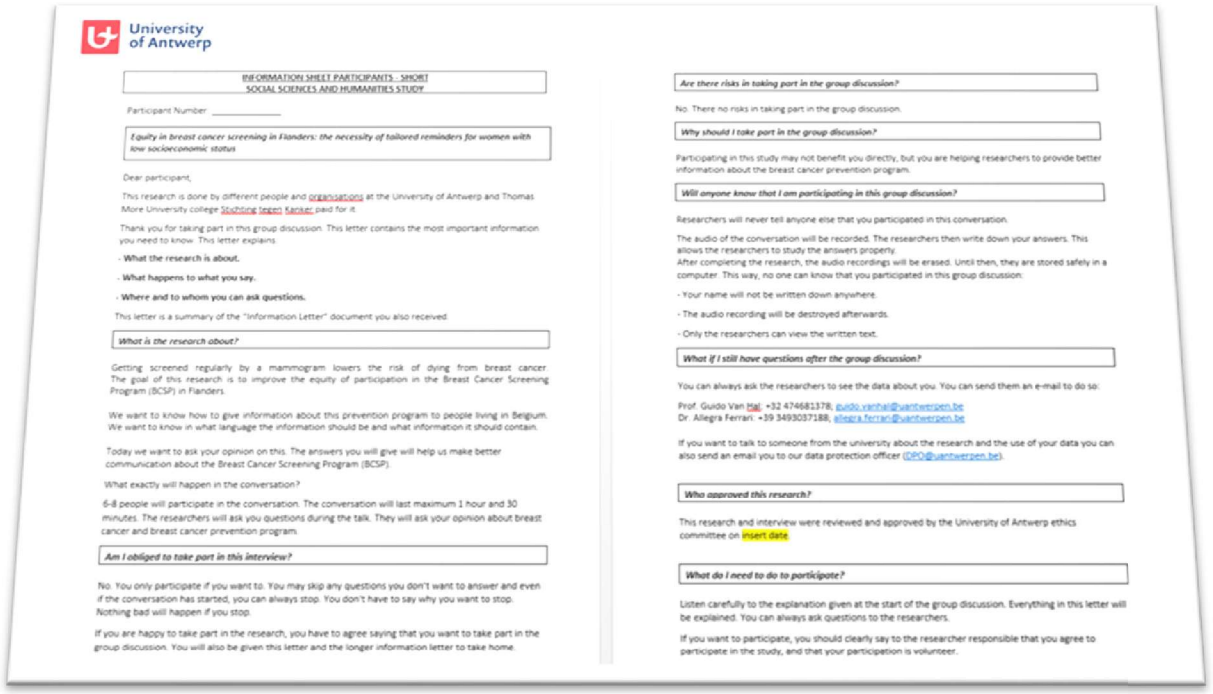
If there are still questions or concerns left, the participants can contact the research coordinator of the project via e-mail or telephone or the Data protection officer (DPO) of the University of Antwerp.
The present researchers will document when participants give verbal consent.

Informed consent procedure

The ICF procedure will be handled by researchers. This will be done as follows:

The researcher writes down on the ICF the name of the participant if the participant approved to participate in the study. This will be done twice on identical ICFs as one will be provided to the participant, and one will be kept for the study's purposes. Data collected will be processed, stored and maintained at the University of Antwerp, according to regulations.

FAC-SIMILE of the simplified information sheet



University of Antwerp

INFORMATION SHEET PARTICIPANTS - SHORT
SOCIAL SCIENCES AND HUMANITIES STUDY

Participant Number: _____

*Equity in breast cancer screening in Flanders: the necessity of tailored reminders for women with low socioeconomic status*

Dear participant,

This research is done by different people and organisations at the University of Antwerp and Thomas More University college Stichting Ieper Kanker paid for it.

Thank you for taking part in this group discussion. This letter contains the most important information you need to know. This letter explains

- What the research is about.
- What happens to what you say.
- Where and to whom you can ask questions.

This letter is a summary of the "Information Letter" document you also received.

***What is the research about?***

Getting screened regularly by a mammogram lowers the risk of dying from breast cancer. The goal of this research is to improve the equity of participation in the Breast Cancer Screening Program (BCSP) in Flanders.

We want to know how to give information about this prevention program to people living in Belgium. We want to know in what language the information should be and what information it should contain.

Today we want to ask your opinion on this. The answers you will give will help us make better communication about the Breast Cancer Screening Program (BCSP).

What exactly will happen in the conversation?

6-8 people will participate in the conversation. The conversation will last maximum 1 hour and 30 minutes. The researchers will ask you questions during the talk. They will ask your opinion about breast cancer and breast cancer prevention program.

***Am I obliged to take part in this interview?***

No. You only participate if you want to. You may skip any questions you don't want to answer and even if the conversation has started, you can always stop. You don't have to say why you want to stop. Nothing bad will happen if you stop.

If you are happy to take part in the research, you have to agree saying that you want to take part in the group discussion. You will also be given this letter and the longer information letter to take home.

***Are there risks in taking part in the group discussion?***

No. There no risks in taking part in the group discussion.

***Why should I take part in the group discussion?***

Participating in this study may not benefit you directly, but you are helping researchers to provide better information about the breast cancer prevention program.

***Will anyone know that I am participating in this group discussion?***

Researchers will never tell anyone else that you participated in this conversation.

The audio of the conversation will be recorded. The researchers then write down your answers. This allows the researchers to study the answers properly.
After completing the research, the audio recordings will be erased. Until then, they are stored safely in a computer. This way, no one can know that you participated in this group discussion.

- Your name will not be written down anywhere.
- The audio recording will be destroyed afterwards.
- Only the researchers can view the written text.

***What if I still have questions after the group discussion?***

You can always ask the researchers to see the data about you. You can send them an e-mail to do so:

Prof. Guido Van Hal: +32 474681378, guido.vanhal@uantwerpen.be
Dr. Allegra Ferrari: +39 3493037188, allegra.ferrari@uantwerpen.be

If you want to talk to someone from the university about the research and the use of your data you can also send an email you to our data protection officer (DPO@uantwerpen.be).

***Who approved this research?***

This research and interview were reviewed and approved by the University of Antwerp ethics committee on insert date

***What do I need to do to participate?***

Listen carefully to the explanation given at the start of the group discussion. Everything in this letter will be explained. You can always ask questions to the researchers.

If you want to participate, you should clearly say to the researcher responsible that you agree to participate in the study, and that your participation is volunteer.

All documents will be translated in Dutch and sent to the EC for approval before the enrollment procedures

## 4. Impact

| Demonstrate the output of the project |
|---|
| The tangible products and services that result from the project.<br>1. A systematic review manuscript of the interventions to increase participation in the BCSP.<br>2. A report of the FGDs about the misconceptions to BCSP of low-SES women in Flanders.<br>3. A co-created reminder that is tailored to tackle the misconceptions to BCSP of non-participantswhich can be used by other BCSPs, be it adapted to their needs.<br>4. Manuscripts regarding the effectiveness and the cost-effectiveness of the tailored reminder in Flanders. |

| Demonstrate the potential outcome of the project |
|---|
| The participation rate in the scheduled screening will be improved by an expected minimum 5%.<br><br>At sector level, the outcome will be evaluated as response rate <92 days following the mammography appointment. At individual level, outcomes will include response rate <92 days following the mammography appointment and attitudes and beliefs towards the BCSP, evaluated by means of Champion's Health Belief Model Scale (CHBMS) and the Breast Cancer Awareness Measurement (BCAM) scale.<br><br>To this aim, participants in the study at the individual level will be asked to fill in a self-administered questionnaire twice, at enrollment, and two weeks after screening by means of a follow-up call. At this time, intentions to participate in the future and reasons for participation/non-participation will also be investigated.<br><br>The life years gained from the improved participation rate by sending the tailored reminder and the cost due to sending the reminder will measured using a validated micro-simulation model and the cost-effectiveness of the tailored reminder in BCSP will be calculated. |

| Estimated number of potential beneficiaries of the project |
|---|
| 31437 |

## 5. Quality

| How will the **quality** of the research and/or the intervention be **guaranteed**? |
|---|
| We will appoint the principal investigator as the project coordinator and set up a steering committee that consists of the representatives of the involved organizations. The coordinator together with the committee is responsible for the practical organization of the project, monitoring the timing, budget, and progress planned, and project reporting according to the regulations of the Foundation against Cancer.<br>Every month, regular meetings with the committee will be organized by the coordinator in order to ensure a continued check of the progress and audit of the quality throughout the entire project. During these sessions, the committee will review the processes used to create the deliverables to determine if the processes seem sound and reasonable. In addition, representatives of the involved organizations will discuss the project's progress and decide upon potential issues and solutions.<br>All the data collected in the project will be well-documented and well-saved based on the checklist for research data management www.nwo.nl/beleid/open+science/datamanagement and stored in a centralized database, which has the function of version control and managing access to personal data. All data will be protected by the General Data Protection Regulations (GDPR), which will inform participants of their rights and anonymize/pseudonymize personal data. |

How will the **follow up** of the project be organized and guaranteed?

The follow-up of the project will be organized by the steering committee led by the study coordinator. One of the main tasks of the committee is the practical organization of the project including the organization of the follow-up of the included women.
Specifically, in the first meeting of the committee, the role of the involved organizations will be clearly communicated. If extra support is needed from the organizations in the committee to tackle the obstacles in the follow-up telephone call, the project coordinator will also organize additional meetings with the committee.
In order to minimize the number of dropouts in follow-up, the project will be clearly explained in meetings for the collection of the informed consent, the self-administrated questionnaire and the telephone number from the women who consent to participate in this study. In these meetings, women will beclearly informed that we will give them a phone call for the follow-up. For women who cannot be reached by telephone, an additional call will be organized by our collaborator CvKO. Moreover, for all women included, small presents such as goody bags as an incentive will be made available.

Which **methodology** will be used to evaluate the project?

Indicators for the evaluation of the effect of the tailored reminders include:
1. The number and the participation rate of the included women in the intervention and control group. We aim to include at least 5% more women in the intervention group into the scheduled BCSP compared with the control group. The participation rate will be calculated by a ratio of the number of participants and the total number of women who received the tailored reminder by mail.
2. The number and the percentage of women in the intervention and control group who intend to participate in the next scheduled screening in two years. We expect at least 5% more women in the intervention group intend to participate in screening than the control group, indicating a sustained impact of the reminder on women in the intervention group.
3. The knowledge and attitude towards BCSP before and after getting the tailored reminder. We aim to create a report for the evaluation of the knowledge and attitude towards BCSP before and after the tailored reminder. The included women will be interviewed with an adapted validated questionnaire before and after the distribution of the tailored reminders by mail. For each question in the questionnaire, the answer before and after receiving the reminder will be collected and compared. Our research team will evaluate the change of the knowledge and attitude towards BCSP with paired t-test for continuous variables and McNemar's test for categorical variables.

Indicators for the evaluation of the cost-effectiveness of the tailored reminders include:
1. Life years gained of women who received the tailored reminders and women in the regular invited group without any reminder.
2.The cost is due to the implementation of the tailored reminder.
A previously developed micro-simulation model will be attuned with the input parameters including the incidence of BC, the all cause mortality of women eligible for screening, the BC specific survival rate of women in screening age in Flanders from the CvKO combined with data regarding the breast tumor volume doubling time, BC clinical detection risk searched from literature. The model will be validated with the comparison between the model estimated number and size of the screen-detected and interval BC in the first and the subsequent screening round with the observed data from the CvKO. The model will be considered as well-validated when the model estimated outcomes are within the 95% confidence interval of the observed outcomes.
The model simulates cohorts in the presence of BCSP with different participation rates due to the implementation of the tailored reminder from a lifetime horizon. The model contains several sub-modules including the life expectancy, BC incidence, natural history of BC, BC screening sensitivity and specificity, BC induction due to radiation risk of mammography screening, BC specific survival, and cost due to BC screening, BC diagnosis, treatment, and the implementation of the tailored reminder. The death age of each woman in the simulated cohort will be determined by life expectancy or cancer-specific survival years (for those developed BC), whichever comes first. In the validated model, the life-years gained will be calculated by the difference of the life years of the screened cohorts with and without the implementation of the tailored reminder. The cost- effectiveness of the two groups with and without the implementation of the tailored reminder will be calculated by the ratio of the life-years gained and the additional cost due to the implementation of the tailored reminder.

## 6. Dissemination of the project

| Demonstrate the further **dissemination** of results. |
| --- |
| According to the theory of the diffusion of innovations, a dual-process dissemination plan that activates both information channels and influences channels will be developed. GPs are one of the information channels of our dissemination plan because they are considered as the credible and trusted source of advice by women in the low SES community. Therefore, we will further disseminate the tailored reminders at GP clinics with the support of Domus Medica. In this passive dissemination approach, the tailored reminder will be demonstrated in prominent positions like the billboard in the GP clinics. GPs do not need to proactively promote the reminder unless women are interested in the reminder demonstrated in the clinics.<br>To accelerate the diffusion of the information of the tailored reminders, we will also collaborate with KRAS to further disseminate the tailored reminder. In the activities they organize in the low SES communities, we will add the tailored reminders into the documents they provide to the low-SES women. We will also try to recruit the women who gained the correct interpretation towards BCSP and participated in the scheduled screening as the lay advocators in the promotion of the BCSP in low SES communities. |

| Where? |
| --- |
| The tailored reminders can be adopted gradually by the BCSP in Flanders based on a developed implementation plan. The tailored reminder will be sent out to the low-SES women by mail in a small number of municipalities and gradually rolled out to the whole region of Flanders. Moreover, the knowledge of the misconceptions to breast cancer screening of the low-SES women eligible for screening will also be used in the educational curriculum of prospective medical doctors (University of Antwerp) and nurses (Thomas More) making this future generation aware of the importance of education and communication to tackle the misconceptions to BCSP. |
| How? |
| We will communicate the results to the policymakers and the general public through multiple ways, in order to implement the tailored reminder into the population-based BCSP in Flanders. Firstly, we will present our results in the meetings of the different Flemish Task Forces regarding cancer screening and the organisation of a cancer screening symposium; Secondary, we will publish the results in international and local peer-reviewed journals; Thirdly, we will improve the awareness with the general population via the website of the Flemish population screening programmes and setting up of a public event. When the policymakers are informed about the effectiveness of the tailored reminders, we will collaborate with CvKO to implement the reminder gradually in the population-based breast cancer screening program. |