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Nationwide cluster-randomised trial of extending the NHS breast screening age range in England

Submission date	Recruitment status	[_] Prospectively registered
15/01/2010	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
22/02/2010	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
21/11/2024	Cancer	[X] Record updated in last year

Plain English summary of protocol
Can be found at: http://www.agex.uk/

Study website
http://www.agex.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

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29856

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NCT01081288

Secondary identifying numbers
10/H0710/9, IRAS 29856

Study information

Scientific Title
Nationwide cluster-randomised trial of extending the NHS breast screening age range in England

Acronym
The AgeX Trial

Study objectives
Current hypothesis as of 28/09/2016
In 1988, the national Breast Screening Programme (BSP) began offering women aged 50-64 years triennial mammographic screening and full national coverage was achieved by the mid-1990s.
In 2003, the age range for triennial screening was extended from 50-64 to 50-70 years; proposals from committees in the Department of Health to randomise this age extension and thereby to obtain reliable information on both the risks and benefits of additional screening at ages 65-70 were not adopted.
Currently, 80 breast screening units cover all of England, each responsible for a defined area, and each year they invite about 2.8 million women aged 50-70, with 2.0 million accepting. The BSP sets standards for the screening units and monitors performance through its national quality assurance network.
In 2007, the Prime Minister announced plans for eventual extension to the range 47-73 years. This offered another opportunity to obtain reliable evidence about the effects of extending the age range of triennial screening. Hence, a trial of this age extension has begun, in which only half are offered extra screening, with the effects monitored through routinely collected NHS statistics.
Following a 2009-10 pilot study of the acceptability of cluster-randomisation of additional screening at ages 47-49 and 71-73 in 5 breast screening units, the AgeX trial extended recruitment to about five-sixths of the breast screening clinics in England, and this cluster-randomisation continues.
In 2011, the Government deferred the earliest possible date when screening would be extended to all women aged 47-73. Later, Public Health England (PHE, which is responsible for government screening programmes) stated that final decisions about extension of the age range would await the emergence of reliable evidence of its effects. The AgeX trial will eventually provide this.
In 2012, an independent panel set up by the Department of Health and the charity Cancer Research UK reported “The UK breast screening programmes [at ages 50-70] confer significant benefit and should continue…. The impact of breast screening outside the ages 50-69 years is very uncertain. The Panel supports the principle of the ongoing trial in the UK [AgeX] for randomising women under age 50 and above age 70 to be invited for breast screening”.
Meanwhile, as female life expectancy is increasing, interest has grown in the possible advantages of continuing to screen women not just in their early 70s but throughout their 70s. The advantages and the disadvantages of continuing triennial screening after age 70 would be

seen more clearly in a trial of 2 or 3 additional invitations (covering ages 71-76 or 71-79) than in a trial of just one.
In 2013 the All-Party Parliamentary Group on Breast Cancer in Older Women (APPG) said "Women are not routinely invited for breast screening past the age of 70 … the current 'age extension trial' [of screening past age 70] … should be extended past 73 to 76, and, if appropriate … further extended". In a separate report in 2015 the APPG reiterated this conclusion.
Although AgeX began as a trial of additional screening at ages 47-49 and at ages 71-73, it has therefore become a trial in which the older women allocated additional screening can, where resources are available, continue be invited triennially at ages 71-76 or at ages 71-79, thereby assessing the effects of continuing triennial screening for several years after age 70.

Current hypothesis as of 17/03/2015:
The NHS Breast Screening Programme routinely invites women aged 50-70 years to come for screening every three years. In 2007 the government decided that the age range for screening would be extended to 47-73 years. Funds were not available for immediate roll-out of screening to all women aged 47-73, and this trial was proposed and agreed. There is uncertainty about the effects of screening outside the 50-70 age range, and the aim of the trial is to assess reliably the risks and benefits of additional invitations for screening before age 50 and, separately, after age 70.
When the extension of breast screening to women aged 47-73 was announced in 2007 the intention was to offer breast cancer screening to all women in this age range after 2012, but in 2011 the date was changed to 2016 at the earliest. Subsequently, Public Health England (now responsible for all screening programmes in England) stated that future decisions about extending routine NHS breast cancer screening outside the age range 50-70 years should await the emergence of reliable evidence as to its effects. This trial can provide this information.
Randomisation of small groups (cluster randomisation) of trial participants determines which groups of women are offered one additional screening invitation before age 50 and which are not, and which groups of women are offered additional screening after age 70 and which are not. So for each separate age range the trial will be able to compare over the following years those women in the clusters invited for screening and those women in the clusters not invited for screening. Women will be followed up by linkage to NHS records, including cancer and hospital records, to assess the risks and benefits of the additional screening. It will take until at least the mid-2020s before results are known.
The findings will be monitored, analysed and reported as two entirely separate trials. One is a trial among younger women (randomly allocated at age 47-49 to additional screening invitation or control) of the effects of an extra screening invitation 3 years before routine screening would normally have begun. The other is a trial among older women (randomly allocated at age 71-73 to additional screening invitation or control) of the effects of an extra screening invitation among those who have had their final routine screening invitation.
The trial began in 2009 and eventually is likely to include at least two million women aged 47-49 and one million aged 71-73. It will involve about 71 of the 81 breast screening units in England. The units expected not to participate are mainly those using non-standard methods for inviting women for screening.

Previous hypothesis:
Currently all women aged 50 - 70 are invited for breast screening every three years. In 2007 the Cancer Reform Strategy announced that from 2012 the NHS Breast Screening Programme (NHSBSP) would cover women aged 47 - 73. As capacity does not allow for full immediate roll out across the whole of England, this age extension is being phased-in with full coverage intended from 2012 although this may now be delayed due to slower than expected introduction of digital mammography.

To date there is limited evidence on the net benefit of extending (up or down) the age range for breast screening; no trial has looked at the added value of one extra screen within an existing screening programme.
This study proposes randomising the phasing-in of the age extension and collecting information on breast cancer incidence and mortality over the following 10 years. This would provide unbiased evidence on the net effects of extending the age range for breast screening. The findings have the potential to inform future screening policy in the UK and elsewhere.
The age extension will proceed regardless of whether this study goes ahead or not, and therefore regardless of whether the phasing-in is randomised or not.
The study builds on the pilot study (Pilot study of the feasibility and acceptability of randomising the phasing-in of the age extension of the NHS Breast Screening Programme in England: ISRCTN50037017) which investigated in several pilot sites the feasibility and acceptability of randomising the phasing-in of the age extension.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Ealing and West London Research Ethics Committee, 22/02/2010, ref: 10/H0710/9
2. North London Research Ethics Committee 3 gave written agreement on 16/12/2010 for a) the trial to be extended for another 3 years and b) inclusion of data from the women in the pilot study (09/H0710/2) in this trial
3. NRES Committee London – Harrow gave written agreement on 8/8/2011 for linkage of breast screening records from the trial to other records (in addition to the cancer and death registration records already included in the original application)
4. In October 2014 the NRES Committee London – Harrow confirmed ethical approval of Substantial Amendment 3 and ongoing ethical approval of the trial. Substantial Amendment 3 covers changes to the trial protocol and the participant information sheet (version 3 and version 3.3, respectively)
5. 01/09/2016: the NRES Committee London – Harrow confirmed ethical approval of Substantial Amendment 4 which covers changes to the trial protocol (v4.1) and the participant information sheet and GP poster (version 4.4 and version 4.2 respectively)

Study design
Multicentre cluster randomized trial

Primary study design
Interventional

Secondary study design
Cluster randomised trial

Study setting(s)
Other

Study type(s)
Screening

Participant information sheet
Available at http://www.agex.uk/links/

Health condition(s) or problem(s) studied
Breast cancer mortality

Interventions
Description of interventions as of 28/09/2016:
Randomisation is by cluster. In the routine BSP, a national database is used to create screening invitation batches, typically every few weeks, for each local breast screening unit. An invitation batch typically lists several hundred women of appropriate age who are recorded (in the local screening database) as registered with the same general practitioner or living in the same geographical locality (e.g., one village, or one part of a town) where the local breast screening unit will next be working. Once generated, this batch is used by the local breast screening unit to invite the women in it for mammography.
Before the trial began, batches would have included women aged 50-70 years (by the end of the current year). During the trial, batches include women aged 47-73 rather than only those aged 50-70; in other words, in addition to the 50-70 age group, they now include the new entrants into the trial, who are the cluster of age 47-49 and the cluster of age 71-73 years.
Each batch is randomly allocated to invite for screening either the trial entrants aged 47-49 or those aged 71-73 years, as shown in the figure. (The women aged 50-70 are unaffected by the random allocation of the batch; they are invited as normal and are not new entrants into the trial). The batch will also include trial participants invited 3 years ago at ages 71-73 (but now aged 74-76) for a second invitation and eventually those invited 3 years ago at ages 74-76 (but now aged 77-79) for a third invitation.
The random allocation of each batch is done by a specially written computer program with equal (50/50) probability and no stratification. A small proportion of women are excluded before randomisation because, for example, they have asked to be withdrawn from the national breast screening programme, are recorded as having had a bilateral mastectomy, or had been screened recently.
Each participant enters the trial on the date when the screening batch she is in is created and randomised; invitations generally go out a few weeks later. New entrants in the batch who are randomly allocated not to be invited join the trial as controls. This is approved by the Confidential Advisory Group.
Women aged 47-49 years who are not to be invited for screening can request to be screened, but the pilot study suggested few will do so. Women over 70, irrespective of the trial, are already able to request screening every three years, but this option is not widely taken up in the general population.

Description of interventions as of 17/03/2015:
As part of the routine breast screening process screening invitation batches are created typically containing several hundred women spanning ages 50 to 70 years. During the trial, batches include women aged 47 to 73 years. Each batch is randomly allocated to invite for screening either the trial entrants aged 47-49 or those aged 71-73 years. For women in the batch who are to be invited for screening, invitations would generally be sent out within a few weeks of the batch being generated. New trial entrants in the batch who are randomly allocated not to be invited join the trial as controls.
Women aged 47 – 49 years in a batch where their age group is randomised not to be invited for screening can request to be screened. Women over 70 are already able to request screening every three years, irrespective of the trial.
The findings will be monitored, analysed and reported as two entirely separate trials. One is a trial among younger women (randomly allocated at age 47-49 to additional screening invitation or control) of the effects of an extra screening invitation 3 years before routine screening would normally have begun. The other is a trial among older women (randomly allocated at age 71-73

to additional screening invitation or control) of the effects of an extra screening invitation among those who have had their final routine screening invitation.

Previous description of intervention:
As part of the routine breast screening process screening invitation batches are created of on average 1,000 women spanning ages 50 to 70 years. With the age extension, slightly larger batches of women aged 47 to 73 years will be created. Each batch will be randomly allocated to one of two groups, that is, to include either women aged 47 - 70 or women aged 50 - 73. Randomisation of the screening invitation batches will be done with equal (50/50) probability and no stratification. Study participants are the women aged 47 - 49 and 71 - 73 in these screening batches; on average, there will be of the order of 200 such women in each batch.
As a result of randomisation half the women aged 47 - 49 and 71 - 73 will be invited for screening at this stage, while the rest will not be invited until full implementation of the age extension. Women aged 47 - 49, who are not invited for screening at this stage will be screened on request if they live in an area that has started extending the age range. Any woman over 70 is already able to request screening every three years.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Description of primary outcome measures as of 28/09/2016
1. The primary analyses among older women will be of breast cancer mortality:
1.1. Up to but not including age 80, and, eventually
1.2. Subdivided by separate time periods (0-4, 5-9, 10-14, etc years after the exact date of randomisation) and by receptor status (ER+, other)
2. The primary analyses among younger women will be of breast cancer mortality:
2.1. Up to but not including age 60, and, eventually
2.2. Subdivided by separate time periods (0-4, 5-9, 10-14, etc years after the exact date of randomisation) and by receptor status (ER+, other)

Description of primary outcome measures as of 17/03/2015:
Breast cancer mortality

Previous description of primary outcome measures:
Mortality from breast cancer by age 60 for women invited to have an additional early screen (before age 50) versus those not invited, and by age 80 for women invited to have an additional late screen (after age 70) versus those not invited

Secondary outcome measures
Description of secondary outcome measures as of 04/10/2016:
1. Breast cancer incidence, up to the same date that the primary outcome (breast cancer mortality) is reported
2. Hospital admissions for mastectomy and lumpectomy, up to the same date that the primary outcome (breast cancer mortality) is reported
3. All-cause mortality, up to the same date that the primary outcome (breast cancer mortality) is reported

Description of secondary outcome measures as of 17/03/2015:
1. Breast cancer incidence
2. Hospital admissions
3. Investigation, detection and treatment of breast lesions
4. Overall and cause-specific mortality

Previous description of secondary outcome measures:
1. Breast cancer registrations in the screened and unscreened groups
2. A range of other medical outcomes, including screening outcomes in women invited for screening

Overall study start date
01/06/2009

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Female
2. Aged 47 - 49 years or 71 - 73 years
2. In a Breast Screening Unit participating in the study. All Breast Screening Units in England are expected to participate in the study with the exception of a few that use non-standard methods for creating screening batches

Participant type(s)
Other

Age group
Adult

Lower age limit
47 Years

Upper age limit
73 Years

Sex
Female

Target number of participants
4,000,000

Total final enrolment
4559280

Key exclusion criteria
Does not meet inclusion criteria

Date of first enrolment
01/06/2009

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Five sixths of the 80 NHS English breast screening units
United Kingdom
-

Sponsor information

Organisation
University of Oxford (UK)

Sponsor details
c/o Heather House
Clinical Trials and Research Governance
Joint Research Office
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Churchill Hospital
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United Kingdom
OX3 7LE

Sponsor type
University/education

Website
http://www.admin.ox.ac.uk/researchsupport/ctrg/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Department of Health funds allocated to Public Health England

Funder Name
Study co-ordination and data analysis is funded from the quinquennial core support for the Cancer Epidemiology Unit and for the Clinical Trial Service Unit (both in the University of Oxford's Nuffield Department of Population Health) from Cancer Research UK and the Medical Research Council

Results and Publications

Publication and dissemination plan
Results will be disseminated in peer-reviewed open-access journals, at medical conferences and on the web. Datasets will be analysed only in anonymised form, and publications will not identify individuals.

Intention to publish date
31/12/2027

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No