Nationwide cluster-randomised trials in England of extending the NHS breast screening age range: protocol for the 2025-33 follow-up phase of AgeX

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Sponsor: University of Oxford
Funding (for follow-up phase): Cancer Research UK

Study participants	Women aged 47-49 and aged 71-73 at entry		
Number randomised	4.5 million		
Planned study period	2009 to 2033		
Randomisation period	2009 to 2020		
	Objectives	Outcome measures	Time-point(s)
Primary	To assess the long-term effects of one additional breast screening visit at age 47-49, and, separately, at age 71-73 on breast cancer mortality	Breast cancer mortality	Final report (2033) on mortality to 12-2031
Secondary	To assess the long-term effects of one additional breast screening visit at age 47-49, and, separately, at age 71-73 on other outcomes	Breast cancer incidence; breast cancer treatment; all-cause mortality	Final report (2033) on incidence to 12-2030; treatment to 12-2029

Summary

Background: In the UK, the nationwide breast screening programme routinely invites women aged 50-70 to come for triennial digital mammography. Because of uncertainty about the effects of screening outside this age range, two cluster-randomised studies (the AgeX trials) are under way to assess reliably the eventual effects of one additional screening before age 50 and, separately, of one additional screening after age 70.

Methods: From 2009-2020, random allocation of small clusters of participants (in a 50:50 ratio) was used to determine which younger women would be invited, or not invited, for one additional screening at age 47-49, and which older women would be invited, or not invited, for one additional screening at age 71-73. In each age range, some 20,000 clusters containing 2.8 million younger women and 1.7 million older women were randomised. To assess the long-term effects (over a decade or two, depending on the year of randomisation) of one additional screening on breast cancer incidence, treatment and mortality, follow-up by electronic linkage to routinely collected NHS records is continuing. Interim and final analyses will report breast cancer mortality to 12.2026 and to 12.2031.

Primary and main subsidiary analyses: The main analyses will be restricted to the 2 million younger women and 1 million older women who, when randomised, were the right age, alive, linkable to routinely collected national records, without any history of cancer or other breast disease, and likely to accept if invited (based on prior acceptance of screening). Among them, adherence-corrected analyses will be used to help assess the effects of one additional screening *visit* at age 47-49, and, separately, at age 71-73. In younger women, the primary analysis will be of mortality after reaching age 55 from a breast cancer diagnosed < 4 years after randomisation. In older women, the primary analysis will be of mortality after reaching age 75 from a breast cancer diagnosed < 4 years after randomisation. The main subsidiary analyses will assess effects on other outcomes. Parallel analyses will assess the effects of being randomly allocated to be invited, regardless of whether an additional screening visit actually took place.

Background

The UK NHS routinely offers all women free triennial 2-view digital mammographic breast screening at ages 50-70, and any NHS treatment arising from this is also free. The advantages and disadvantages of starting at a somewhat earlier age are uncertain. Likewise, there is uncertainty about the advantages and disadvantages of continuing to a somewhat later age.

In 2007, the Prime Minister announced eventual extension of NHS breast screening from ages 50-70 to 47-73[1], but it was unclear when this would begin. This offered an opportunity for AgeX to obtain large-scale randomised evidence about the effects of one additional screening.

During 2009-20 Age X has randomly allocated 20,000 clusters of women aged about 47-49 to be offered, or not, one additional screening invitation and, separately, 20,000 clusters of women aged 71-73 to be offered, or not, one additional screening invitation.

Follow-up is only through linkage to routine records held centrally by NHS England, which will help assess the effects of one additional screening on breast cancer mortality (the primary endpoint), on breast cancer incidence, and on the eventual use of radiotherapy and chemotherapy.

In 2011, the Government deferred the date for extending the screening age range[2]. 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 about 50-70] confer significant benefit and should continue…. The impact of breast screening [outside this age range] is very uncertain. The Panel supports the principle of the ongoing trial[s] in the UK [AgeX] for randomising women under age 50 and above age 70 to be invited for breast screening"[3].

In 2013 Public Health England became responsible for government screening programmes, and stated that final decisions about extension of the age range would await the emergence of reliable evidence of its effects, and in 2018 an independent enquiry into the nationwide delivery of breast screening had reported that AgeX should continue "until its planned end in 2026"[4], with formal Government statements in both Houses of Parliament then accepting this recommendation[5,6]. In 2021, NHS England replaced Public Health England.

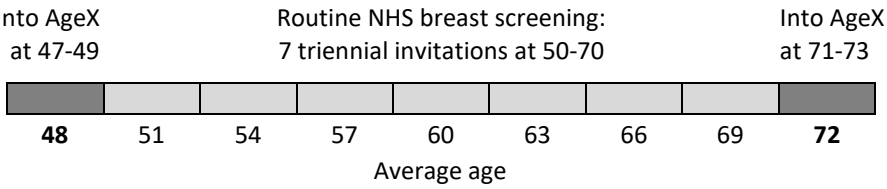
Although AgeX randomisation was to continue until 2026, in March 2020 it ended following the suspension of all breast screening due to COVID. Interim and final analyses will report breast cancer mortality to 12.2026 and to 12.2031. This ensures the eventual length of follow-up will be about one or two decades (depending on the year of randomisation).

The design and follow-up of AgeX remain similar to what was envisaged in the linked protocol for the randomisation phase, with the few differences outlined in Annex 1. This protocol is for the 2025-33 follow-up phase of AgeX, after randomisation of 4.5 million women during 2009-20 and consolidation of the database during 2021-24. This consolidation included identifying for the main analyses the 3 million women who had been eligible and were linkable to NHS England datasets, with no prior record there of cancer or breast disease, and who were considered likely to attend screening if invited (as they had attended their previous breast or cervical screening invitation). Since AgeX began, the dataset has been held securely, with access to any personal identifiers strictly restricted even within the study team (Annex 2).

Randomisation (2009-20)

When randomisation ended, some 20,000 clusters of women aged 47-49 had been randomly allocated to be invited or not for one additional screening about 3 years before the first of their 7 routine invitations. Likewise, some 20,000 clusters of women aged 71-73 had been randomly allocated to be invited or not for one additional screening about 3 years after the last of their 7 routine invitations (Figure 1).

Figure 1: AgeX randomisation of one additional screening in younger and in older women



Randomisation procedures

Women were included in AgeX if they were aged 47-49 or 71-73 and registered with at GP surgery covered by a breast screening unit participating in the study. (Around five-sixths of breast screening units participated in AgeX).

The routine screening programme used a national database to create screening invitation batches, perhaps every few weeks, for each local breast screening unit. An invitation batch typically listed several hundred women of appropriate age (usually 50-70 if not participating in AgeX and 47-73 if participating) who were recorded as currently registered with a particular general practice or living in the locality (eg, one village, or one part of a town) where the breast screening unit was currently working. As each particular locality would not be covered again for about 3 years, the first routine invitation should have occurred at age 50-52 and the last at age 68-70.

The program that generated these batches was updated during 2016-18 to use each woman's exact age in completed years. (Before then it had used an estimate of age obtained by subtracting the year of birth from the current year: for details, see Annex 3). In batches prepared for AgeX, the program identified new entrants into AgeX, who were those in the cluster aged 47-49 and those in the cluster aged 71-73.

As each batch was being prepared for AgeX, the program preparing it randomly allocated (with equal 50:50 probability and no stratification) either AgeX entrants aged 47-49 or those aged 71-73 to be invited for screening, as shown in Figure 1. The women aged 50-70 were unaffected by the random allocation of the batch; they were invited as normal, and were not new entrants into AgeX.

Lists of those randomised were forwarded to the AgeX investigators, after complete removal by the NHS of any invitees or controls who had previously opted out of having their NHS records used for research or who had been classified as unsuitable for a screening invitation (perhaps because of bilateral mastectomy or a record of having recently been screened).

Each participant entered AgeX on the date her screening batch was created and, simultaneously, randomised; invitations generally went out a few weeks later. New entrants in the batch who had been randomly allocated not to be invited joined AgeX as controls.

Trial participant information

Screening units informed local general practitioners that AgeX was taking place in their area, and a poster about AgeX (Annex 4) was provided for them to display in their surgery. Otherwise, the controls were not individually notified.

Where randomisation into AgeX was in progress, women of any age who were being sent an invitation for screening all received the standard NHS screening brochure plus the AgeX participant information sheet (Annex 5), which said that if they were aged 50 to 70 then they could ignore the leaflet. It also said that if they were younger than 50 or were 71 or older then they were being sent the invitation (which they were free to ignore) as part of a trial of breast screening in which their de-identified routine NHS records would be analysed by researchers at the University of Oxford.

Consent and confidentiality

Section 251 approval for including women in AgeX without consent and for the use of patient-identifiable data without consent was obtained initially from the UK National Information Governance Board for Health and Social Care, then annually from it and any successor (currently the Health Research Authority Confidentiality Advisory Group, CAG). With respect to consent for screening, the standard procedures of the NHS breast screening programme applied, whereby attending screening was taken as implied consent.

Linkage of individual records is to routinely collected data, currently held centrally by NHS England. AgeX is conducted in accordance with all relevant aspects of CAG, General Data Protection Regulation, and the Data Protection Act requirements. All datasets continue to be treated appropriately, held securely, used only for medical research, and analysed only in de-identified form. Further details of data handling and security are provided in Annex 2.

Consolidation of the AgeX database (2021-24)

In 2021, screening was completed of all participants (including those delayed by COVID). Data linkage had been disrupted by the pandemic and by the replacement in 2021 of Public Health England by NHS England. By 2024, however, data linkage to all relevant NHS records had been re-established and the whole database had been consolidated, defining the pre-randomisation characteristics only from sources that could not have been affected by the random allocation.

Data linkage

During randomisation, the National Breast Screening System (NBSS) and, later, Breast Screening Select (BSS) provided information on new AgeX participants. Identifiers such as name, NHS number and date of birth were included for secure (Annex 2) onward linkage to several other sources:

- NHS screening records (for information about screening history);
- Death and cancer registry data, including the Cancer Outcomes and Services Dataset (for information on cause-specific mortality and details of incident cancers, including tumour histology, size, stage, grade, nodal involvement and receptor status);

- NHS Hospital Episode Statistics (for information on cause-specific hospital admissions and procedures, including systemic breast cancer treatments, particularly chemotherapy, and surgery, particularly mastectomy);
- The Systemic Anti-Cancer Therapy data set (for information on chemotherapy)
- The Radiotherapy Dataset (for information on radiotherapy); and
- Data approved for anonymous transfer from the nationwide prospective Million Women Study (for information on quality of life).

Such routine records, all but the last of which are currently being provided to AgeX by NHS England, will cease if women decide to opt out of having their further NHS records used for research or emigrate.

Reporting of results to 12.2026 and to 12.2031

Long-term follow-up is necessary to assess the eventual effects of one additional screening on breast cancer incidence, treatment, and, particularly, mortality. As little effect on breast cancer mortality should be expected until years 5-9 and 10-14 after randomisation, prolonged follow-up of mortality will be required, first to the end of 2026 (with the first mortality report due in 2027-28) and then to the end of 2031 (with the final mortality report due in 2032-33).

Follow-up of breast cancer incidence and treatment will be reported in 2025-26, before any unblinded analyses of mortality are reported, but electronic follow-up of breast cancer incidence and treatment will continue after that date. The final report on mortality will be accompanied by updated analyses of breast cancer incidence and treatment, and by health economic analyses.

At least annually, the data monitoring and ethics committee will continue during follow-up to review confidential analyses, particularly of mortality. It can recommend the release of results earlier than scheduled if clear answers emerge.

Statistical analysis

A detailed statistical analysis plan is provided separately (Annex 6). The principal features of the main analyses are as follows.

Analysis as two separate trials

The findings will be monitored, analysed and reported as two separate trials. One is a trial among younger women (randomly allocated at age 47-49 to one additional screening invitation or control). The other is a trial among older women (randomly allocated at age 71-73 to one additional screening invitation or control).

Restriction to 2 million younger women and 1 million older women

Of the 4.5 million women randomised, only 3.0 million are included in the main analyses population. Women were included only if, when randomised, they were the right age, alive, linkable to routinely collected NHS England electronic records, without a history of cancer or other breast disease, and likely to accept if invited (based on their previous screening history). All these criteria were based unbiasedly on information recorded before randomisation and were chosen blind to analyses of mortality differences between invitees and controls. None of these criteria excluded significantly different proportions of invitees and controls.

Effects of actually having one additional screening VISIT

The primary and main subsidiary analyses will be of the effects of actually having one additional screening **visit** (from adherence-corrected analyses: see next section).

Parallel analyses will also be provided of the effects of being randomly allocated to receive one additional screening **invitation** (from intent-to-treat analyses). These under-estimate, perhaps by about one-quarter, the effects of actually having an additional screening. For, the difference between invitees and non-invitees in the proportions actually screened was about three-quarters, both in younger women and in older women.

Primary and main subsidiary endpoints

The primary endpoint is breast cancer mortality (based only on the certified underlying cause of death). The main subsidiary endpoints are invasive breast cancer (overall, and subdivided by tumour characteristics such as diameter, grade, ER status and stage), in situ breast cancer, use of mastectomy, use of systemic breast cancer therapy (particularly chemotherapy), and use of radiotherapy for breast disease.

Mortality from a breast cancer diagnosed < 4 years after randomisation

A few years after just one single additional screening invitation, the annual incidence rates of newly diagnosed breast cancer may well become similar in invitees and in controls. No material effect of the random allocation should be expected on mortality from breast cancers that are diagnosed after this convergence of incidence rates, so the mortality analyses focus on deaths from breast cancers that had been diagnosed only a few years after randomisation.

Mortality after younger women reach age 55 and older women reach age 75

No material effect of the random allocation should be expected on breast cancer mortality during the first few years after randomisation. Hence, the primary analyses are restricted to the later breast cancer deaths.

Primary analyses

The primary analyses will be of the effects of one additional screening visit on numbers of deaths from a breast cancer diagnosed < 4 years after randomisation that occurred after reaching age 55 (for younger women) or after reaching age 75 (for older women).

Although the primary analyses will disregard oestrogen receptor (ER) status, corresponding analyses of mortality from ER+, ER– or ER unknown breast cancer will also be given.

Main subsidiary analyses

The main subsidiary analyses will be of breast cancer incidence and treatment. Additional subsidiary analyses will investigate any effects of screening on other outcomes that are available from linkage with routinely collected NHS records. The final primary and subsidiary analyses will be accompanied by appropriate health economic analyses. Analyses of other mortality and all-cause mortality will be given, but uninformative.

Allowance for cluster randomisation

Although AgeX is cluster-randomised the primary analyses of breast cancer mortality will average only about 0.1 breast cancer deaths per cluster, so they will have virtually the same statistical power as individually randomised comparisons of similar size would have had.

Adherence-corrected analyses of the effects of one additional VISIT

Estimates of the effect of one additional screening visit will use the method of Cuzick et al[7] to allow for non-adherence, which avoids assuming similarity between those adherent and non-adherent to the random allocation. Adherence-corrected analyses estimate the effects of one additional screening visit among those women who would have had a screening visit if, and only if, randomly allocated to be invited for screening. (Screening does not include mammography after a breast cancer has been diagnosed.)

Some women, who may well be atypical in unknown but relevant ways, would not get screened, regardless of what their random allocation happened to be. Some other women, perhaps atypical in other relevant ways, would get screened anyway, again regardless of what their random allocation would be. All others would have a screening visit if, and only if, randomly allocated to be invited. *

		Randomly allocated to be sent a screening invitation?	
		Yes	**No**
Actually had a screening visit?	**Yes**	**A.** Screenee, adherent to allocation	**B.** Screenee, not adherent to allocation
	No	**C.** Non-screenee, not adherent to allocation	**D.** Non-screenee, adherent to allocation

Adherence-corrected analyses of the effects of actually having, vs not having, a screening visit involve comparing (A – B) vs (D – C), with groups A, B, C and D as defined in the table. For, subtraction of group B is equivalent to removing from group A those who would have been screened even if not invited, leaving those who would have a screening visit if, and only if, invited. Likewise, subtraction of C is equivalent to removing from D those who would not have been screened even if allocated to be invited, again leaving those who would have a screening visit if, and only if, allocated to be invited. *

This comparison of (A – B) vs (D – C) assesses unbiasedly the full effects among those who would have a screening visit if, and only if, allocated to be invited, without assuming that groups A, B, C and D are comparable with each other. This method of adjustment for adherence has little or no effect on the statistical power to detect any differences in breast cancer mortality between invitees and controls.

***** There might also, at least in theory, be a tiny group who, perversely, would all get exactly the opposite of whatever their random allocation happened to be. Ideally these non-adherent women would be excluded when analysing the results, but as they are not individually identifiable they cannot be. This does not, however, introduce any bias at all into the adherence-corrected estimates of the proportional effect of screening (as the adherence correction subtracts this tiny non-adherent group from both sides of the comparison).

Trial management group

The management group includes clinicians, screening specialists, epidemiologists, trialists, health economists, geneticists, lay members, and the investigators. It confers about yearly, or more frequently if needed, to monitor progress and consider any relevant new information, including any reports or recommendations from DMEC.

Data monitoring and ethics committee (DMEC)

The DMEC is independent of the trial management group and oversees safety, efficacy and ethical issues, including any arising from new information from other sources. It normally confers about yearly, and can request any extra meetings or data analyses it considers appropriate. All investigators (other than the statistician and statistical consultant) remain blind to all the mortality data, but the DMEC reviews unblinded mortality data at each of its meetings. Its terms of reference are:

- Advise the trial management group on any ethical issues, and respond to any ethical concerns raised about (or by) AgeX. Such concerns should generally be communicated first to the trial coordinator, but can be sent directly to the DMEC chair.
- Advise the management group if, in DMEC's opinion, there is proof beyond reasonable doubt* that an additional screening invitation at age 47-49 or at age 71-73 is definitely appropriate or definitely inappropriate for some or all identifiable categories of women.
- Communicate directly with the Director of Research Services of the University of Oxford (as study sponsor) if the DMEC considers any ethical issues not to have been resolved.

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* Appropriate criteria are not pre-specified, but as potentially relevant breast cancer and other deaths continue to accumulate for many years after entry to AgeX, a highly statistically significant difference in breast cancer mortality might well be required by the DMEC to justify release of mortality results earlier than scheduled.

Publication and dissemination

Results will be disseminated in peer-reviewed open-access publications, at conferences, and online. The AgeX investigators and AgeX Public Advisory Group will co-create press releases, lay summaries and infographics, and multimedia content such as podcasts and short videos, for traditional and social media platforms. This and other dissemination by the investigators will not involve recommendations for or against screening.

Following the interim reports on breast cancer incidence and treatment, and on breast cancer mortality, the intent is to release a dataset sufficient to assess the robustness of published findings. When the final analyses are reported the intent is for the entire analysable dataset to be made available immediately. The investigators will obtain the appropriate permissions to share AgeX data.

Ethical and regulatory considerations

Approvals

Ethical approval for AgeX was given in 2010 and again in 2016 by Ealing & West London (now Harrow) Research Ethics Committee (ref 10/H0710/9). Section 251 support for use of patient-identifiable data without consent and for access to medical records by those outside the healthcare

team was approved by the National Information Governance Board Ethics & Confidentiality Committee and is reviewed annually by the Health Research Authority Confidentiality Advisory Group, CAG (ref ECC 1-04 (b)/2010, IRAS ID 29856).

The chief investigator will submit and, where necessary, obtain approval from the Sponsor, the research ethics committee, CAG and NHS England for all substantial amendments to the trial protocol.

Reporting

The chief investigator will submit once a year, or on request, a progress report to the Sponsor, CAG, NHS England, and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties and the REC and Health Research Authority.

Protocol deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

Serious breaches

A "serious breach" is a breach of the protocol that is likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the research. If a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the chief investigator, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving research ethics committee and NHS England within seven calendar days.

Finance and insurance

Department of Health and Social Care funds were allocated to Public Health England for the additional screening for AgeX. The trial analyst and trial co-ordinator are currently funded by Cancer Research UK. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). Appropriate contractual arrangements will be put in place with all third parties.

Archiving

Once the study has ended, it is anticipated that de-identified study data will be archived on NDPH file servers for at least 25 years.

Participating breast screening units City, Sandwell & Walsall; Dudley & Wolverhampton; Hereford & Worcester; North Staffordshire; Shropshire; South Birmingham; South Staffordshire; Warwickshire, Solihull & Coventry; Nottingham; North Nottinghamshire; Lincoln; North Derbyshire; South Derbyshire; Leicester; Kettering; Northampton; Newcastle; North Tees; North Cumbria; Humberside; Pennine; Leeds Wakefield; North Yorkshire; Barnsley; Doncaster; Rotherham; Sheffield; South Essex; Bedfordshire & Hertfordshire; Epping; Chelmsford & Colchester; Southampton & Salisbury; Isle of Wight; North and Mid Hampshire; Portsmouth; Aylesbury & Wycombe; Milton Keynes; East Berkshire; West Berkshire; Oxfordshire; Bolton; Chester; Crewe; East Lancashire; Greater Manchester; Liverpool; East Cheshire & Stockport; North Lancashire; Warrington & Whiston; South Lancashire; Wirral; Avon; Cornwall; Dorset; Gloucestershire; Somerset; South Devon; West Devon & East Cornwall; Wiltshire; Barking, Havering, Redbridge & Brentwood; Central & East London; North London; South East London; South West London; West London; East Sussex, Brighton & Hove; Jarvis, Guildford; West Sussex, Worthing; Canterbury, Medway & Maidstone.

Investigators AgeX was planned and conducted throughout its randomisation phase by researchers from the Cancer Epidemiology Unit and from the Early Breast Cancer Trial Collaborative Group, both of which are part of the University of Oxford Nuffield Department of Population Health (NDPH). AgeX continues to be conducted by researchers from NDPH and the current investigators are: Associate Professor Toral Gathani (chief investigator); Associate Professor Isobel Barnes (deputy chief investigator); Krys Baker (AgeX co-ordinator); Dr Gurdeep Mannu; Associate Professor Hongchao Pan (AgeX statistician); Professor Julietta Patnick; Professor Richard Peto (statistical consultant); Professor Gillian Reeves; Keith Shaw (AgeX data manager); Professor Carolyn Taylor; Associate Professor Jane Wolstenholme.

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Data Monitoring and Ethics Committee Professor Stephen MacMahon (Chair), Founding Director, George Institute for Global Health (trialist, epidemiologist); Professor Abdel Babiker, MRC Clinical Trials Unit, University College, London (trialist, statistician); Dr Ros Given-Wilson, St Georges Hospital, London (consultant breast radiologist); Professor Alison Halliday, Nuffield Department of Surgery (surgeon, surgical trialist); Ms Jenny Rusby, Royal Marsden Hospital, London (consultant breast surgeon).

Trial Management Group Julietta Patnick (chair); Krys Baker (co-investigator); Isobel Barnes (deputy chief investigator); Jillian Boreham (lay member); Clare Borelli, NHS Breast Screening Programme (radiographer); Philip Clarke, NDPH (health economist); Toral Gathani (chief investigator); Robert Hills, NDPH (statistician); David Hunter, NDPH (epidemiologist); Anneke Lucassen, University of Oxford Nuffield Department of Medicine (clinical geneticist); Gurdeep Mannu (co-investigator); Hongchao Pan (co-investigator); Richard Peto (co-investigator); Malcolm Reed, Brighton and Sussex Medical School (surgical oncologist); Gillian Reeves (co-investigator); Keith Shaw (co-investigator); Carolyn Taylor (co-investigator); Sian Taylor-Philips, Warwick Medical School (population health researcher); Suzanne Wright, Intelligence and Research Lead, NHS England; Louise Wilkinson, NHS National Speciality Adviser for Breast Screening and Consultant Radiologist; Jane Wolstenholme (co-investigator).

Further information is available from the AgeX website.

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Annex 1: Changes to the previously described study design and follow-up

Partly to increase statistical power, randomisation of older women between more than one additional screening invitations and no additional invitations was originally envisaged, but the additional work required was not practicable for the screening program, so the AgeX trial involves only *one* additional invitation.

The routine assignment of underlying causes of death to breast cancer (ICD-10 C50 or ICD-11 2C6) or to other 3-character ICD categories by the Office of National Statistics will be accepted without further investigation. It was originally envisaged that all possible deaths from breast cancer would be reviewed, but this has not been attempted for any deaths so far, and will not be. For, attempts by the investigators to refine ONS cause of death assignments would have been expensive, time consuming, and incomplete, would have had little effect on statistical power, and could have engendered unjustified concerns about possible effects of investigator biases.

To increase sensitivity of the primary analyses and make the subsidiary analyses relevant to them, these analyses were all to be limited to the women of appropriate age who could be linked to national statistics, had no prior cancer or breast disease, and were likely to accept an invitation if randomly allocated to receive one. The details of these analyses (which are given in the statistical analysis plan) could not, however, be finalised until after recruitment had ended and linkage to all relevant national databases had been attempted. It was done blind to any mortality analyses.

The protocol for the randomisation phase of the trial envisaged that, when sufficient follow-up was available, subdivision of the findings for breast cancer mortality by 5-year groups of time since randomisation would supersede the previously planned subdivision by whether the deaths were before or after age 60 for younger women (or 80 for older women). Because the age range of randomisation is extremely narrow, the present subdivision of mortality by 5-year age groups achieves both purposes, and has been adopted blind to any mortality analyses.

Interim and final analyses will report mortality to 12.2026 (with the first mortality report due in 2027-28) and then to the 12.2031 (with the final mortality report due in 2032-33). The final mortality report, will be accompanied by health economic analyses.

Annex 2: Data handling and physical security

Records are processed securely within the Nuffield Department of Population Health (NDPH), with the University of Oxford as sponsor and data controller. Data security complies with the Data Protection Act (University of Oxford: registration Z575783X) and NDPH and University data security policies. NDPH has current NHS data security protection toolkit accreditation for storage of linked NHS data (ref: EE133863-MSD-NDOPH-NDPH); relevant data security and governance policies are available on request. Files are stripped of identifiers (name, address, date of birth, NHS number) before any data analyses. All working on AgeX are legally bound not to identify participants. Datasets with identifiers can be accessed only by those responsible for data linkage and de-identification, not by the study investigators or analysts. People analysing the de-identified dataset have only read access to it, and have no access to any other part of the database, and cannot link the IDs used in it to any other part of the database. The study is expected to continue until around 2033, after which the data will be de-identified and retained in accordance with the funder's requirements for at least 25 years.

Electronic records are held securely in secure buildings with swipe card access on all external doors, which are monitored by CCTV. Visitors and deliveries report to reception for verification. High-security areas such as server rooms are physically separate from other facilities, have additional security locks, and are restricted to relevant staff. Offices are locked outside normal working hours. The NDPH IT disaster recovery plan covers responses to environmental and external threats. Server rooms have air conditioning to ensure servers operate within limits specified by the manufacturers and are supplied from multiple mains feeds, with equipment split between feeds, and are protected by uninterruptible power supply units (UPS) to prevent corruption of information, with a back-up generator in case of prolonged power outage. The internal telephones system provides 24-hour access to on-site security staff and public emergency services.

Annex 3: Effects of changing the details of the definition of the age range in 2016-18

The seemingly trivial distinction between *birth-year age* (current year minus birth year) and *birthday age* caused problems with breast screening that were not clearly recognised until 2018. If this year's birthday has already happened then these two ages are the same, otherwise the birthday age is 1 less than the birth-year age; on average, therefore, it is 6 months less.

When 3-yearly breast screening began in 1988 England was divided into about 80 areas, each with its own screening unit. Over the subsequent decades, few areas changed. The large majority of units adopted a 3-year cycle, reviewing successive GP lists and inviting the women on each list according to *birth-year age* (50-70, since the mid-2000s). So, birth-year age could equally well have been 50, 51 or 52 at the first invitation, and 68, 69 or 70 at the last.

Hence, 1/3 of all women in these areas got their first invitation at birth-year age 50, at a time when half (ie, 1/6 of all women) had not yet reached their 50th birthday. Likewise, 1/3 got their last invitation at birth-year age 68, at a time when half (1/6 of all women) had not yet reached their 68th birthday. 3 years later these women, being of birth-year age 71, would not be invited again, although still of birthday age 70. This affected about 1/6 of all women reaching age 70, and was later considered inappropriate.

Although breast screening invitations traditionally depended on birth-year age, and continued to do so, new wording introduced by Public Health England (PHE) in 2013-14 inadvertently specified the upper age limit in terms of *birthday age* (by saying that 3-yearly screening would continue "until the 71st birthday"). It was not realised that changes in invitation procedures were implied, but from then on a discrepancy existed, affecting substantial numbers of women per year, between what the invitation procedures were doing and what they were said to be doing.

During 2018 there was much concern about use of birth-year age 50-70 rather than birthday age 50-70 to decide who to invite, but it should be noted that it made no difference to the frequency or total number of invitations. On average it made invitations start, and so end, younger by 6 months of age, but there is no good evidence as to whether this was better or worse for women.

In 2009, AgeX began randomising whether or not to continue inviting women who would otherwise have been just too old to be invited, which at that time meant those of birth-year age 71-73. (It also began randomising whether or not to offer an additional invitation at younger ages.)

In July 2016 new PHE software was introduced that, in addition to inviting birth-year age 50-70, provided the *option* (not always used) of also inviting women of birth-year age 71 who were still of birthday age 70. This software should have ensured that use of this option would exclude such women from AgeX (as half would get no invitation), but it did not. This was the only relevant IT error; there was no error in 2009, when the trial began.

From July 2016 to January 2018 some women of birthday age 70 entered the trial. During 2018 those allocated no further screening were informed by PHE that they could still request screening, and most were also offered a specific 2018 screening appointment. As most women of birthday age 70 who entered the trial after mid-2016 would get an invitation regardless of their allocation, all are excluded from the primary analyses (but will be reported on separately).

Early 2018 concerns about women of age 70 not being offered an invitation centred at first on the trial, even though it had never had any involvement with, or access to, the patient invitation software. Enquiries later in 2018 clarified the fundamental role of the inadvertent discrepancy (which was unrelated to AgeX) between what the patient invitation software had been doing ever since the UK screening program began and the newly prepared 2013-14 specification.

This discrepancy has since been resolved; since September 2018, invitations are based on birthday age. This means the first invitation should arrive at birthday age 50, 51 or 52 (on average 6 months later than it used to) and the last should arrive at birthday age 68, 69 or 70 (again, on average 6 months later than it used to). It also means that women entering AgeX since September 2018 are of birthday age 47-49 or of birthday age 71-73. (NB To allow for delays before screening, randomisation selects ages 46 years 8 months to 49 years 10 months.)

Annex 4: Information poster about the trial, which was to be displayed in GP surgeries

Breast Screening Programme

Your local breast screening team is now working in this area, inviting the women aged about 50-70 who are registered in this practice for routine breast screening.

A research trial is also being done to help assess the benefits and risks of screening women slightly younger than 50 and older than 70.

For this research, about half the women aged 47-49 and half of those aged 71-73 are also being sent letters inviting them for screening, plus a leaflet giving them information about the trial.

Women invited by the trial for screening at age 71-73 may well be invited again at ages 74-76 and 77-79.

To assess the effects, screening data will be linked to routinely collected health records held by NHS Digital for all women, whether or not they were invited. Names will be removed before researchers analyse the data.

Further information about the trial and data flow, including information about how to opt out of the study, can be found at www.agex.uk

You can discuss breast screening with your doctor.

All women aged over 70 can ask to be screened while the screening team is in the area, regardless of the trial. If you want to do this, the practice staff can help.

Nationwide cluster-randomised trial of extending the breast screening age range in England: the AgeX trial. Original ethical approval: Ref 10/H0710/9

Annex 5: Patient information sheet (which was 4 pages)

AgeX: Trial of extending the age range for breast screening to include some women aged under 50 or over 70

Why have you been sent this leaflet?

Women of ages about 50 to 70 in the UK are normally invited for breast screening every three years.

This leaflet tells you about a research study* taking place across most of England of the risks and benefits of extending breast screening to women slightly younger or older than the usual 50 to 70 age range.

If your age is 50 to 70 you are not being invited to take part in the trial, but are being offered routine breast screening. You don't need to read this leaflet any further.

If you are younger than 50, or if you are 71 or older, we are inviting you for screening as part of this trial. Please read this information sheet.

* Nationwide cluster-randomised trial of extending the breast screening age range in England: the AgeX trial (formerly called the Age Extension Trial, with original ethical approval Ref 10/H0710/9, and ongoing approval confirmed in September 2018)

Why do we need a trial?

While we know a lot about the effects breast screening has for women aged about 50 to 70, there is not enough evidence on the effects for women aged somewhat less than 50 or over 70. This trial will assess the risks of screening (in particular, the chances of being diagnosed and treated for a non-life-threatening cancer) and benefits (in particular, the chances of saving life) for these slightly younger and older women.

The trial began in 2009 and is still recruiting women. By late 2018 there were already four million women in the trial, and eventually there will be substantially more. It will, however, take until at least the mid-2020s to get reliable information, like that for women aged 50 to 70 years shown in the enclosed brochure 'NHS breast screening, Helping you decide'. The findings will help the UK government decide whether or not to widen the age range for routine breast screening.

[continued on next page]

What happens if you agree to take part?

In the area where you live, we are selecting half the women aged 47 to 49 and half the women aged 71 to 73 and inviting them for screening. This is done by allocating groups of women (clusters) at random, like tossing a coin, either for the whole group to be invited for screening, or for the whole group not to be invited. (A typical cluster might involve a few dozen or a few hundred women who live near each other.)

The study can then compare over the following years what happens to those women in the clusters invited for screening and what happens to those women in the clusters not invited for screening. Any woman who accepts the invitation will be screened in the normal way.

Possible risks and benefits

The enclosed brochure 'NHS breast screening, Helping you decide' describes the screening process and discusses the risks and benefits of screening women at ages 50 to 70 years. Equivalent information for younger or older women is not as reliably known, especially about the long-term benefits that screening is intended to provide.

Although earlier detection should make treatment easier, most women who get asked to return for more tests will not have breast cancer. The trial will record the investigations and treatments received by all women, to determine the risk of having any unnecessary treatment.

Before age 50, about 15 out of every 200 women screened get asked to return for more tests, but on average only about one of them will be found to have breast cancer. So, about 1 in every 200 screens before age 50 will result in a breast cancer being found.

After age 70, only about 7 out of every 200 women screened get asked to return for more tests, but on average about two of them will be found to have breast cancer. So, about 2 in every 200 screens after age 70 will result in a breast cancer being found.

The brochure says screening prevents about 1 breast cancer death for every 200 women screened regularly from ages 50 to 70. Since UK women are offered about 7 screens between age 50 and 70, the number quoted in the brochure is the equivalent of about 1 death prevented per 1400 screens.

For each screen just before 50 or after 70, however, there might well be a somewhat lower or a somewhat higher than 1 in 1400 chance of avoiding death from breast cancer. The trial is designed to give reliable information about what those chances really are.

What medical records will be used?

Your screening records will be linked, using information such as your name and date of birth, to routinely collected data held by NHS Digital on hospital admissions and cancer. This will allow researchers to assess the risks and benefits of the extra screening.

Once linked, however, all these records will be made anonymous so the researchers using them will not be able to identify any individuals. A research team at the University of Oxford is organizing the trial and analyzing the data.

What happens if you don't want to take part?

If you don't want to accept this invitation, then please let your local breast screening unit know that you are unable to attend. If you are aged 71 or older you will not be invited again for routine screening as that stops at 70, but you can still ask to be screened if you wish. If you are under 50 you will still be invited for routine screening in about 3 years time.

Where can you find out more about this trial and about breast screening?

For further details see www.AgeX.uk or ask your GP.
www.AgeX.uk gives further information about the trial, data privacy,
how trial information is handled or used, and how to opt out if you wish.
www.gov.uk/topic/population-screening-programmes/breast
gives further information about the Breast Screening Programme.
Funded by the Department of Health and Social Care
[2025 note: This statement about funding was correct during recruitment, ie, from 2009-2020.]

Annex 6: Statistical analysis plan (currently given as a separate document)