

# **Nationwide cluster-randomised trial of extending the NHS breast screening age range in England: AgeX trial protocol**

## **Summary**

**Background:** In the UK, the nationwide Breast Screening Programme routinely invites women aged 50-70 years to come for triennial screening. Because of uncertainty about the effects of screening outside this age range, a cluster-randomised trial (AgeX) is under way to assess reliably the risks and benefits of extra screening before age 50 and, separately, of extra screening after age 70.

**Methods:** Random allocation of small clusters of participants is used to determine (in a 50:50 ratio) which women are offered one additional screening invitation before age 50 and which are not, and which women are offered additional screening after age 70 and which are not. The AgeX trial will involve about five-sixths of the 80 breast screening units in England. For some years it will randomise women who reach the age range 47-49 to be invited or not for one additional screen before reaching the age range 50-70, and will randomise women who reach the age range 71-73 to be invited or not for up to 3 additional screens. Women will be followed up by electronic linkage to routine government records to assess the short-term and long-term effects of additional screening on: patterns of investigation, detection and treatment of breast lesions; breast cancer incidence; breast cancer mortality; hospital admissions and procedures; and overall mortality. The trial is registered, ISRCTN33292440 and NCT01081288.

**Principal and subsidiary analyses:** The principal analyses will be restricted to those women among whom, based on information recorded prior to the random allocation, an invitation would be likely to have made them attend for screening if they would not otherwise have done so. Among them, analyses by allocated treatment will be used to help assess the effects of extra screening before age 50 and, separately, after age 70 on breast cancer mortality, eventually subdivided by ER status and 5-year time periods (0-4, 5-9, 10-14 years, etc) since random allocation. Subsidiary analyses will assess effects on other outcomes.

**Sponsor** University of Oxford

**Funding** UK Department of Health, Public Health England, UK Medical Research Council, Cancer Research UK.

\* Participating breast screening units are listed at the end of the protocol

## **Introduction**

In England, free triennial mammographic breast screening is routinely offered at ages 50-70 to all women, and any treatment arising from this is also free. The advantages and disadvantages for women of starting mammographic screening at a somewhat earlier age are uncertain. Likewise, there is uncertainty about the advantages and disadvantages of continuing for some years beyond age 70.

AgeX addresses these questions by randomly comparing different age ranges for routine triennial screening invitations in most of England, monitoring any effects on treatments and on outcomes through government statistics.

## **Background**

In 1988, the national Breast Screening Programme (BSP) began offering women aged 50-64 years triennial mammographic screening (1), and full national coverage was achieved by the mid-1990s (9).

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 (10). 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 (2). 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 (3, 4), 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 (5). 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” (6).

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”(7). In a separate report in 2015 the APPG reiterated this conclusion (8).

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.

### **The AgeX trial**

The cluster-randomised AgeX trial will assess reliably the risks and benefits of offering an extra screening invitation to women aged 47-49 (who will all be offered routine screening anyway three years later) and, separately, of offering up to 3 additional triennial invitations to women after age 70 (who will already have been offered routine triennial screening at ages 50-70). Linkage with routinely collected government records will help assess the short-term and long-term effects of the additional invitations on breast cancer incidence, patterns of treatment, breast cancer mortality, and other outcomes.

This trial is embedded within the routines of the BSP, which currently uses two-view digital mammography. Other than randomisation, all aspects of screening will be conducted exactly as normal in the BSP, following its routine procedures. No direct contact with participants will be made by the research team, and the statistical analyses and reports will be of anonymised data.

#### *Participating breast screening units*

The trial will involve about five-sixths of the 80 NHS English breast screening units. The units not participating are mainly those with staff limitations or other operational issues, such as use of non-standard methods for creating screening batches (the unit of randomisation: see below). The breast screening units that participated in the pilot study have become part of the main AgeX trial.

#### *Trial entry by cluster-random allocation of small batches*

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 (eg, 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<sup>1</sup>). 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 National Information Governance Board.

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 (4). 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 (4).

#### *Number of trial participants*

The total number of women entering the trial (half invited for additional screening and half not) is not a fixed sample size. If substantial uncertainty still persists, randomisation may well continue.

#### *Information for participants*

All women invited for screening in a randomised batch, regardless of their age, receive the trial participant information sheet with their invitation for screening along with the standard BSP brochure describing the screening process and providing further information.

#### **Data collection and storage**

Datasets are held at the Cancer Epidemiology Unit in the University of Oxford and are stored securely in accordance with the Data Protection Act and with the Cancer Epidemiology Unit's procedures and policies. The datasets will be anonymised before statistical analyses are undertaken.

---

<sup>1</sup> Age by end of current year is generally used in batch creation; analyses, however, use exact age. As the small area covered by one batch is visited only once every three years, exact age at the first routine screening invitation varies over the 4-year range 49-52 (centred on 51.0) years.

The National Breast Screening System provides information on the trial entrants that includes the patient identifiers needed for record linkage. Trial participants' records are linked electronically to:

- NHS and PHE screening records (for screening history and information about procedures done and diagnoses);
- death and cancer registry data, including both the NHS Digital and the PHE Cancer Outcomes datasets (for information on cause-specific mortality and details of incident cancers, including tumour histology, size, stage, grade, nodal involvement and receptor status, as well as on treatments such as chemotherapy and radiotherapy); and
- NHS Hospital Episode Statistics, held by NHS Digital (for information on cause-specific hospital admissions and procedures, including surgical treatments such as mastectomy, lumpectomy, axillary clearance, etc).

Such routine records cease if women are notified as emigrating, on which date their trial follow-up is censored, but this will probably affect fewer than 1% of participants per decade.

Deaths of women with any history of breast cancer will be reviewed, blind to the random allocation, by an Endpoint Committee to determine whether this was a breast cancer death (defined, because of the difficulty of determining the exact cause of death, to include all deaths with uncontrolled life-threatening breast cancer thought to have been present). These breast cancer deaths provide the principal endpoint of the trial, which is breast cancer mortality.

For each probable breast cancer death, trial organisers will seek a narrative of the diagnosis and treatment of that cancer. This will include the date on which a relevant breast abnormality was first found, how it was found and investigated, the date of diagnosis of breast cancer and the characteristics of the cancer at the first diagnosis (including histology, size, nodal spread, distant spread and receptor status).

## **Analysis plan**

### *Analysis as two separate trials*

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 up to 3 extra screening invitations among those who have had their final routine invitation.

### *Primary analyses*

The primary analyses among older women will be of breast cancer mortality

- a) Up to but not including age 80, and, eventually,
- b) 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).

The primary analyses among younger women will be of breast cancer mortality

- a) Up to but not including age 60, and, eventually,
- b) 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).

In younger women deaths from breast cancer diagnosed after the first routine screen at age 50-52 would not be expected to be affected by the random allocation and hence will be uninformative. To achieve greater sensitivity, the primary analyses will consider separately these uninformative breast cancer deaths and all other breast cancer deaths, if this can be done reliably without introducing any material bias between the two arms of the trial.

In both age ranges most deaths will be from causes other than breast cancer. Although results on mortality from other causes (and from all causes) will be reported, there is expected to be insufficient power for crude analyses of all-cause mortality to assess reliably the effect of additional breast screening on all-cause mortality.

For reasons of statistical power, therefore, the most reliable estimate of the effect of additional screening on all-cause mortality may well come from combining the effects on breast cancer mortality (and any procedural mortality) estimated from this trial with the small long-term effects of medical radiation estimated from other studies, assuming no other effects on mortality.

It is expected at present that first results of the primary analyses will be released for peer review in the mid-2020s and that thereafter observations will continue and more definitive findings released periodically. If at any stage, however, the Data Monitoring and Ethics Committee should advise that there is proof beyond reasonable doubt that additional screening at age 47-49 years or throughout the 70s is appropriate without any material adverse effect on other mortality, the results would be submitted promptly for peer review.

#### *Main subsidiary analyses*

The plausibility of the assumption of no material effects on other mortality will be checked by subsidiary analyses of cause-specific mortality, interpreted with due allowance for the effects of chance when multiple endpoints are analysed. Although subsidiary analyses of all-cause mortality will also be reported, they will not contribute to the primary analysis of breast cancer mortality.

The main subsidiary analyses will be of the details of breast cancer incidence and of the patterns of breast cancer investigation and treatment. Information on screening outcomes, such as recall and biopsy rates, will be collected not only for the women randomised to extra screening invitations but also for the first routine screening invitations at ages 50-52. In addition, many other outcomes available from linkage with routine NHS records will be assessed.

#### *Exclusions from primary analyses and main subsidiary analyses*

The primary and main subsidiary outcome analyses will exclude: duplicate randomisations; women whose NHS records could not be flagged; women who before randomisation had already withdrawn from the BSP; women who had

already died or were known from prior records (ie, objective records before randomisation) to have moved away from the address held by the National Breast Screening System; and women known from prior records to have had cancer (except non-melanoma skin cancer), breast disease, or breast surgery.

Of the others, a proportion of those invited will not take up the screening invitation; this non-uptake will dilute crude analyses of the effect of the invitation on breast cancer mortality. Hence, to reduce this dilution and increase statistical power, women who did not take up their previous cancer screening invitation will be excluded from the primary and main subsidiary analyses, as will other categories of women who are found from prior records to have been unlikely to accept a screening invitation if it had been sent to them at the address provided when the screening batch was created. This will be done using only information that is unbiased with respect to the random allocation.

In women aged 71-73 years at randomisation, a strong predictor of acceptance of an invitation for breast screening is previous attendance for breast screening at their last routine invitation. Likewise, in women aged 47-49 at randomisation a reasonable predictor of acceptance of an invitation for breast screening could well be prior attendance for routine cervical screening.<sup>2</sup>

#### *Statistical power*

*Women aged 47-49:* The median exact age of the women randomised in their late 40s will be about 48.0 years. Among one million women during the 2010s with no breast cancer before age 48.0 who are randomly allocated not to have a screening invitation before age 51.0, about 1500 might be expected to die before age 60 from a breast cancer diagnosed at or before their first routine screening invitation 3 years later. If an additional screen at age 48.0 would reduce this by 15% to 1275 expected deaths, then an evenly randomised trial among 2 million such women with perfect compliance (100% uptake) with all invitations would reliably detect this expected difference of 225 relevant deaths.

With 4 million evenly randomised but with a more realistic uptake rate of only two-thirds (and negligible self-referral among those not invited), the expected difference would be 300 relevant deaths (2700 vs 3000, with standard error 75 and hence a 92% chance of achieving  $2p < 0.01$ ).

The principal analyses will be restricted to those women among whom, based on information recorded prior to the random allocation, an invitation would be likely to have made them attend for screening if they would not otherwise have done so. This somewhat increases statistical power, as does longer follow-up (12). Intra-cluster correlation has little impact on the power calculations, as the screening batches are so small (median about 100 women aged 47-49, in the pilot study) that hardly any will have more than 1 woman with a breast cancer diagnosed at or before routine screening began that causes death.

---

<sup>2</sup> Routine breast screening statistics for England indicate that 88% of women aged 65-70 who had attended for a mammogram in the previous five years take up their next invitation for breast screening, as compared with only 6% for previous non-attenders (10). Likewise, survey data (11) suggest women who had accepted a previous cervical screening invitation were substantially more likely to accept a first invitation for breast screening than those who had not.

*Women aged 71-73:* Among one million women during the 2010s who had been screened at age 69.0 with no relevant abnormality detected, and who still had not been diagnosed with breast cancer by age 72.0, about 4000 might be expected to die of a subsequent breast cancer before age 80. If an additional screen at age 72.0 would reduce this by 15% to 3400 deaths, then in an evenly randomised trial of 2 million such women with perfect compliance (100% uptake by those invited and no self-referral among other women) the expected difference would be 600 relevant deaths, ensuring a highly significant result.

But, with a more realistic uptake rate of 70% of those invited and a realistic self-referral rate of about 10% of those not (as many women in their 70s have become used to being screened), in a trial of 2 million such women the expected difference would be only about 360 relevant deaths (3580 vs 3940, with standard error 87 and hence a 94% chance of achieving  $2p < 0.01$ ).

Again, however, the principal analyses will be restricted to those women among whom, based on information recorded prior to the random allocation, an invitation would be likely to have made them attend for screening if they would not otherwise have done so, which somewhat increases statistical power, as does longer follow-up and additional screening invitations at ages 74-79.

### **Consent, confidentiality and trial supervision**

Women invited for screening will be informed in the trial participant information sheet that the age extension is randomised so that the effects of extending the age range for breast screening can be evaluated reliably, and that the data will be analysed by research workers at the University of Oxford, who are responsible for the organisation of the trial.

Section 251 approval for including women in the trial without their consent and for the use of patient-identifiable data without consent was obtained from the National Information Governance Board for Health and Social Care. With respect to consent for screening, the standard procedures of the NHS Breast Screening Programme apply, whereby attending screening is taken as implied consent. Women aged 47-49 who are randomised not to be invited for an additional early screening can request screening, if they wish. Women aged over 70 in the general population are already able to request screening every 3 years.

Screening units inform local General Practitioners that the trial is taking place in their area and a poster about the trial is displayed in their surgery (Annex 1). The Breast Screening Programme informs women and their GPs of the outcome of screening. Women invited for screening in this trial will be treated in exactly the same way.

Individual records will be linked to NHS Digital and PHE datasets, but will be anonymised once data linkage has been completed. The trial will be conducted in accordance with all relevant aspects of the Data Protection Act and the Health Research Authority Confidentiality Advisory Group (and previously, the National Information Governance Board) requirements. The data will be treated with appropriate confidentiality, and used only for medical research.



Datasets are held securely at the Cancer Epidemiology Unit in Oxford, and are stored in accordance with CEU data storage procedures and policies. Datasets will be analysed only in anonymised form, and publications will not identify individuals. Results will be disseminated in peer-reviewed open-access publications, at medical conferences and on the web.

#### *Data Monitoring and Ethics Committee*

The data monitoring and ethics committee, which is independent of the trial team, will oversee safety, efficacy and ethical issues, including any that arise from new information from other sources. It will confer no less than about once a year, and can request extra meetings at any times it considers appropriate. Progress reports and data will be provided when it confers, and it can demand any analyses or information it considers appropriate to inform its decisions. The terms of reference of the data monitoring and ethics committee are to:

- Advise the trial management group on any ethical issues that arise;
- Respond to any ethical concerns that are raised about the trial (although such concerns should generally be communicated first to the trial coordinator, they can be communicated directly to the chair of the committee);
- Advise the trial management group if, in the opinion of the committee, there is at any stage proof beyond any reasonable doubt that an additional screening invitation at age 47-49 years or throughout the 70s is not appropriate for some or all identifiable categories of women; and, finally,
- Advise the trial management group if, in the opinion of the committee, there is at any stage proof beyond reasonable doubt<sup>3</sup> that additional screening invitations at age 47-49 years or after age 70 is appropriate for some or all identifiable categories of women and will reduce breast cancer mortality by age 60 or by age 80 without any material adverse effect on other mortality.

#### *Trial Management Group*

The trial management group includes breast cancer clinicians, breast screening specialists, medical statisticians, epidemiologists, clinical trialists, a lay representative, and the trial investigators, and will provide overall supervision. Its terms of reference are: Review periodically and guide the progress of the trial, including adherence to the protocol, patient safety and consideration of new information. Meetings will be held at regular intervals determined by need, but no less than about once a year. Routine business can be conducted by email and post. Throughout the trial, it will take responsibility for: major decisions (eg, need to change the protocol for any reason); monitoring and supervising progress; reviewing relevant information from other sources; and considering recommendations from the data monitoring and ethics committee.

---

<sup>3</sup> Appropriate criteria are not pre-specified, but as potentially relevant breast cancer and other deaths continue to accumulate for many years after entry to the trial, an extremely statistically significant (e.g.  $p < 0.0001$ ) difference in breast cancer mortality would probably be required by the committee to justify halting recruitment prematurely in either age group.

## **Further Information**

### **Trial participant information sheet**

Women invited for screening under the Breast Screening Programme receive with their screening invitation the standard BSP patient brochure. Women of any age, whether or not they are in the trial, who are being invited for screening in an area where the trial is in progress receive with their invitation whatever version of the standard BSP patient brochure is current, together with the trial participant information sheet (Annex 2).

**Approvals and permissions** Ethical approval in 2010, 2014 and 2016 for AgeX (formerly called the Age Extension Trial) was from 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 from the National Information Governance Board Ethics & Confidentiality Committee (ECC 1-04 (b)/2010). Additional approvals were granted for the five breast screening units that participated in the pilot study to become part of the main trial, and for linkage of breast screening records from the trial to other records (in addition to the cancer and death registration records included in the original application).

**Sponsor** University of Oxford

**Funding** Department of Health funds are allocated to Public Health England for this trial. 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 the Medical Research Council and Cancer Research UK.

**Investigators** Professor Julietta Patnick (principal investigator), visiting professor, Cancer Epidemiology Unit, University of Oxford; Krys Baker (trial co-ordinator), Cancer Epidemiology Unit, University of Oxford; Professor Dame Valerie Beral, director, Cancer Epidemiology Unit, University of Oxford; Kath Moser (trial epidemiologist), Cancer Epidemiology Unit, University of Oxford; Professor Sir Richard Peto (trial statistician), co-director, Clinical Trial Service Unit, University of Oxford; Professor Sir Mike Richards, Chief Inspector of Hospitals and formerly National Cancer Director; Keith Shaw (trial analyst), Cancer Epidemiology Unit, University of Oxford.

**Data Monitoring and Ethics Committee** Professor Janet Darbyshire (Chair), former director of MRC Clinical Trials Unit (trialist, epidemiologist, medical doctor); Dr Ros Given-Wilson, Medical Director, St Georges Hospital, London (breast radiologist); Professor Tom Meade, London School Hygiene & Tropical Medicine (trialist, epidemiologist, chair of his institute's ethics committee, 2001-08); Dr Gillian Reeves, Cancer Epidemiology Unit, University of Oxford (statistical epidemiologist); Ms Jenny Rusby, Royal Marsden Hospital, London (consultant breast surgeon).

**Trial Management Group** Julietta Patnick (chair and principal investigator); Krys Baker (trial co-ordinator); Valerie Beral (co-investigator); Clare Borrelli, NHS Breast Screening Programme (radiographer); Lucy Carpenter (lay member);

Kevin Fenton, Director of Health and Wellbeing, Public Health England (public health epidemiologist); Jackie Jenkins, National Programme Manager for Breast Screening, Public Health England; Iain Lyburn, NHS Breast Screening Programme (radiologist); Kath Moser (co-investigator); Hongchao Pan, Clinical Trial Service Unit, University of Oxford (statistician); Richard Peto (co-investigator); Professor Malcolm Reed, Dean of Brighton and Sussex Medical School (surgical oncologist); Mike Richards (co-investigator); Keith Shaw (trial analyst); Margot Wheaton (programme manager of Warwickshire, Solihull & Coventry breast screening service).

**Registration** NCT 01081288 (<http://clinicaltrials.gov/ct2/show/NCT01081288>)  
ISRCTN 33292440 (<http://www.controlled-trials.com/ISRCTN33292440>)

**Acknowledgements** This trial will take more than a decade to answer the questions it addresses. We thank the women who participate and the staff of the participating breast screening units for their collaboration. We also thank Amanda Ramirez, Sarah Sellers, Robin Wilson and Richard Winder, who were members of the original Trial Management Group.

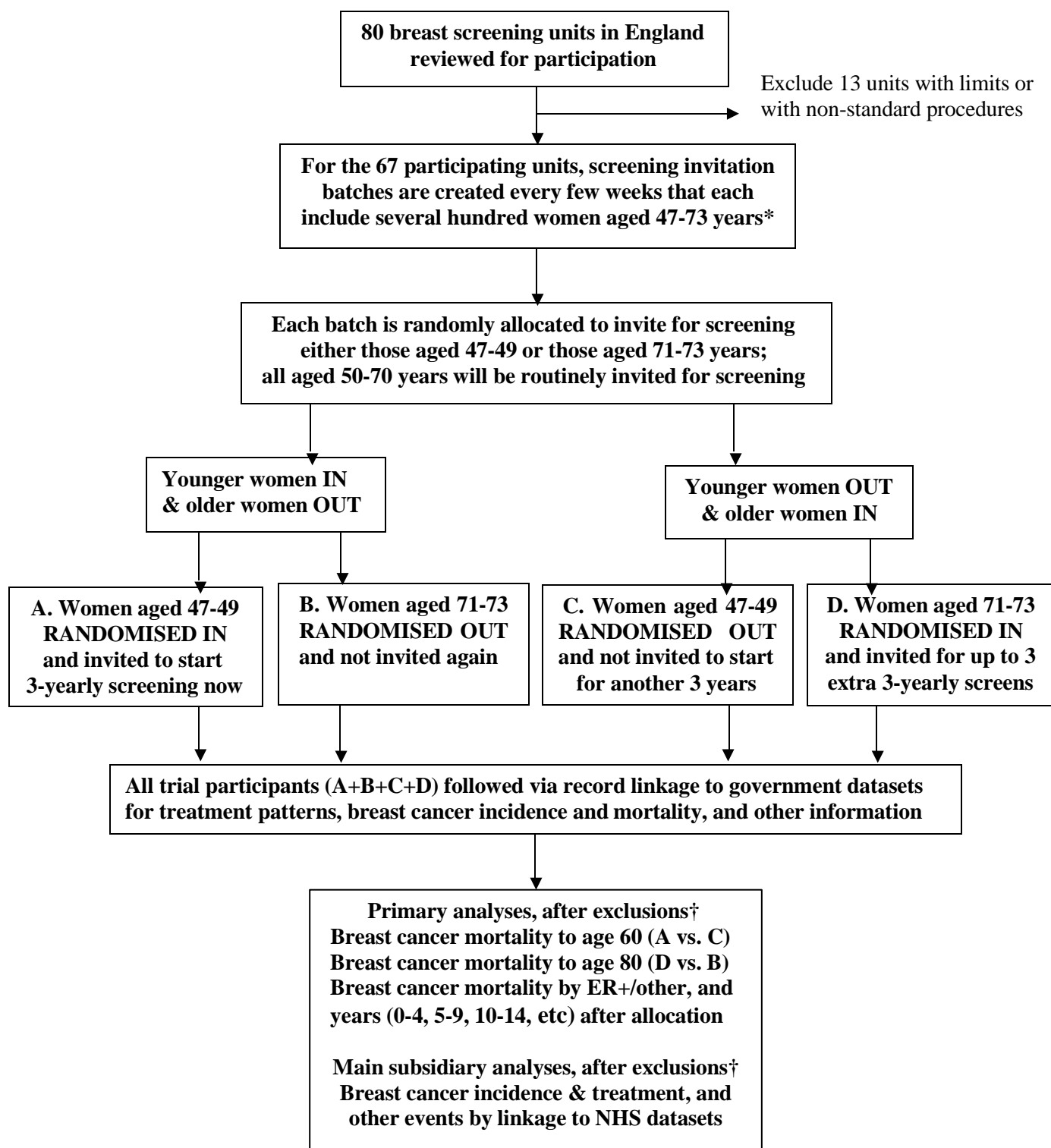
#### **Participating breast screening units**

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.

## References

1. Department of Health and Social Security. *Breast Cancer Screening: Report to the Health Ministers of England, Wales, Scotland and Northern Ireland by a working group chaired by Professor Sir Patrick Forrest*. DHSS: 1986.
2. *Cancer Reform Strategy*. London, Department of Health, 2007  
<http://www.nhs.uk/NHSEngland/NSF/Documents/Cancer%20Reform%20Strategy.pdf>
3. Pilot study of the feasibility and acceptability of randomising the phasing-in of the age extension of the NHS Breast Screening Programme in England <http://www.controlled-trials.com/ISRCTN50037017>  
<http://clinicaltrials.gov/ct2/show/NCT00890864?term=NCT00890864&rank=1>
4. Moser K, Sellars S, Wheaton M, Cooke J, Duncan A, Maxwell A, Michell M, Wilson M, Beral V, Peto R, Richards M, Patnick J. Extending the age range for breast screening in England: pilot study to assess the feasibility and acceptability of randomisation. *J Medical Screening* 2011; 18: 96-102.
5. *Improving Outcomes: A Strategy for Cancer*. London, Department of Health, 2011  
[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_123371](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123371)
6. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; 380: 1778-86.
7. All Party Parliamentary Group on Breast Cancer, 2013. Age is just a number.  
<http://www.stevebrine.com/downloads/age-is-just-a-number-full-report.pdf>
8. All Party Parliamentary Group on Breast Cancer, 2015. Two years on: Age is still just a number. <http://www.stevebrine.com/downloads/bc-age.pdf>
9. NHS Breast Screening Programme  
<http://www.cancerscreening.nhs.uk/breastscreen/index.html>
10. Breast Screening Programme, England: Statistics for 2014-15. Leeds: Health and Social Care Information Centre, 2014 <http://www.hscic.gov.uk/catalogue/PUB13567/bres-scre-prog-eng-2012-13-rep.pdf>
11. Moser K, Patnick J, Beral V. Inequalities in reported use of breast and cervical screening in Great Britain: analysis of cross sectional survey data. *British Medical Journal* 2009; 338: b2025.
12. Beral V, Alexander S, Duffy S, et al. The number of women who would need to be screened regularly by mammography to prevent one death from breast cancer. *J Medical Screening* 2011; 18: 210-12.

**Figure: Flow diagram of randomisation, follow-up and principal analyses**



\* In this flow diagram, age means age by the end of the current calendar year. 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 those invited 3 years ago at ages 74-76 (but now aged 77-79) for a third invitation.

† Exclude from the primary and main subsidiary outcome analyses: duplicate randomisations; NHS records could not be flagged; withdrawn from BSP; already dead or moved from screening clinic's catchment area; or objective prior record of cancer, breast disease, or breast surgery.

‡ Exclude from the primary and main subsidiary analyses women who from objective prior (ie, pre-randomisation) records would be unlikely to accept screening if randomly allocated to it (eg, those who had not taken up their previous screening invitation – see text).

## 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](http://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.

## **Annex 2: Trial participant information leaflet**

Versions of this leaflet in languages other than English, and a large print version, are available from the NHS Breast Screening Programme at <https://www.gov.uk/topic/population-screening-programmes/breast>

# **Trial of extending the age range for breast screening to include some women aged under 50 or over 70 (the “AgeX trial”)**

## **Why have you been sent this leaflet?**

Women of ages 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 will be 50 to 70 at the end of this year 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 will be younger than age 50 or older than 70 at the end of this year, we are inviting you for screening as part of this trial. Please read about the trial on the other side of this 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 ethical approval confirmed in 2014 and 2016)

## **Why do we need a trial?**

While we know a lot about the effects breast screening has for women aged 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 2016 there were already three million women in the trial and eventually the trial will be substantially larger. It will, however, take until at least the mid-2020s to get reliable information like that for women aged 50-70 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.

## **What happens if you agree to take part?**

In the area where you live, we are randomly 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. So for each separate age range the study can compare over the following years what happens to those women in the clusters invited for screening and 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.



Before age 50, about 15 out of every 200 women screened will be 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 is likely to result in a breast cancer being found.

After age 70, only about 7 out of every 200 screens results in the woman being 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 is likely to 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 50-70. Since UK women are offered 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 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 organising the trial and analysing 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 over 70 at the end of this year 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 aged 47 to 49 at the end of this year, you will still be invited for routine screening in about 3 years time.

Women aged 47 to 49 who are not invited or initially decline this invitation but then change their mind can still ask to be screened if they live in an area that is participating in the trial. Most areas in England are taking part in the trial, except for a small number unable to do so for organisational reasons.

For further details see [www.agex.uk](http://www.agex.uk) or ask your GP

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

[www.gov.uk/topic/population-screening-programmes/breast](http://www.gov.uk/topic/population-screening-programmes/breast) gives further information about the Breast Screening Programme

[www.agex.uk](http://www.agex.uk) gives further information about the trial, about how trial information is handled or used, and about how to opt out, if you wish

Leaflet version 4.1 (August 2016).

Funded by Public Health England; the Breast Screening Programme is part of Public Health England.

For further copies of this title visit [www.orderline.dh.gov.uk](http://www.orderline.dh.gov.uk) (quote code **xxxxx**) or contact the DH publications orderline **0300 123 1002** (minicom **0300 123 1003**)