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 about 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 (in a 50:50 ratio) is used to determine 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 involves about five-sixths of the breast screening units in England. It randomises 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 a trial invitation would be likely to determine whether or not they would actually be screened. 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 the oestrogen receptor (ER) status of the breast cancer and by five-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

Chief Investigator: Dr Toral Gathani

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* Investigators and participating breast screening units listed at end of protocol

INTRODUCTION

In England, free triennial mammographic breast screening is routinely offered at ages about 50-70 to all women, and any treatment arising from this is also free. The advantages and disadvantages 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 about 50-64 years triennial mammographic screening (1), and full national coverage was achieved by the mid-1990s (10). In 2000 it was announced that the age range for triennial screening would be extended from 50-64 to 50-70 years. This change began to be implemented in 2004, and was completed within a few years.

Currently, about 80 breast screening units cover all of England, each responsible for a defined area. Each year they invite about 2.8 million women aged about 50-70, with about 2.0 million accepting (11). 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), but it was unclear when this would begin. This offered an 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 units in England, and this cluster-randomisation continues.

In 2011, the Government deferred the date when screening would begin to be extended to all women aged 47-73 (5). 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 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).

In 2013, Public Health England (PHE) became responsible for all government screening programmes, and stated that final decisions about extension of the age range would await the emergence of reliable evidence of its effects. In 2015 (in response to a Parliamentary committee report on NHS screening) the Government stated that the AgeX trial would need to continue to invite women for at least two more [triennial] screening rounds [ie, at least 6 more years] (7).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.

Hence, 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" (8), and in a separate report in 2015 the APPG reiterated this conclusion (9).

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, if screening resources become available, continue to 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 about 47-49 (who will all be offered routine screening anyway about 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 about 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.

Recruitment procedures

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 (delays in which can slightly affect the exact ages at which invitations arrive). No direct contact with participants will be made by the research team, and the statistical analyses and reports will be of anonymised data.

The breast screening units in the 2009-10 pilot study became part of the main AgeX trial, as did most other NHS breast screening units in England. All use the same system of generating screening invitations (described below); the units not participating were mainly those using somewhat different systems, or with staff limitations or other operational issues.

A national database is used to create screening invitation batches, perhaps every few weeks, for each local breast screening unit. An invitation batch typically lists several hundred women of appropriate age who are recorded 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. As this particular locality will not be visited again for about 3 years, the first routine invitation may well be somewhat after age 50, and the last somewhat before age 70.

The program that generates these batches was updated during 2016-18 to use each woman's exact age. (Before then it had estimated age by subtracting the year of birth from the current year[1]). In addition to the 50-70 age group, which will be offered routine screening invitations regardless of whether they are already in the trial, the program also identifies 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 could 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.

PHE (NHS England is now responsible for the breast screening programme) does the random allocation of each batch by their own specially written computer program with equal (50/50) probability and no stratification. (Lists of those randomised are eventually forwarded to the trial investigators.) A few 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 Confidentiality Advisory Group (CAG).

Results are examined regularly by the Data Monitoring and Ethics Committee, and when clear answers emerge they will be published. The total number of women entering the trial (half offered additional screening and half not) is not a fixed, pre-determined sample size. If substantial uncertainty still persists, entry into the study may well continue.

Trial participant information

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 2). The BSP 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.

Women invited for screening under the BSP receive with their screening invitation the standard BSP patient brochure. Women of any age, whether or not in the trial, who are 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, plus the trial participant information sheet (Annex 3). This explains that the data will be analysed by research workers at the University of Oxford, who are responsible for the organisation of the trial.

[1] Annex 1 describes the effects of changing the details of the definition of the age range

Physical security

AgeX records are stored in the Richard Doll Building, a secure building within the Nuffield Department of Population Health (NDPH) at The University of Oxford Old Road Campus. Swipe card access is present on all external doors. External doors are monitored by CCTV. Visitors and deliveries are required to report to the Reception for verification by Reception staff, and all NDPH employees are encouraged to challenge anyone they don't recognise in order to confirm identity and authorisation. High security areas (e.g. server rooms) are physically and electrically separate from other NDPH facilities and have additional security locks in place. Access is restricted to relevant staff. Offices are secured by door locks out of normal working hours when not in use. Open plan work space is secured by internal doors with additional swipe card or proximity card access. Response procedures to environmental and external threats (such as fire, flood and explosion) are covered in the NDPH IT Disaster Recovery Plan. Server rooms have air conditioning units to ensure that the servers operate within operating limits specified by the equipment manufacturers. Offices are secured by door locks out of normal working hours and when not in use. Richard Doll Building server room power is supplied from multiple mains feeds, with equipment split between feeds. Main servers and other key hardware are protected by uninterruptible power supply units (UPS) in order to maintain service in the event of a power outage and prevent corruption of information. A back-up generator provides additional cover in the event of a prolonged power outage. The Big Data institute (BDI) server room has a single UPS system with two separate circuits. Each rack has two power supply units fed from each circuit, power is taken from the least loaded distribution strip in the rack. All NDPH staff have access to on-site security staff as well as public emergency services through the internal telephone system.

Data collection and handling

AgeX records are processed securely within the Nuffield Department of Population Health (NDPH). The University of Oxford acts as Sponsor and Data Controller. Data security complies with the Data Protection Act (University of Oxford: registration number Z575783X) and with Unit, Departmental and University data security policies. The 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 from the study team. All recruitment data and linked follow-up data are stored separately with restricted access within the study team, and used to prepare de-identified datasets for analysis. Access to identifying information provided by participants (name, address, date of birth,) is restricted within the study team. Files are stripped of identifiers such as name or NHS number before any data analyses. All those working on data are bound by legal agreement not to identify participants, and where possible data are provided in a form which minimises this risk (eg. tabulations, or suppressing part of birth date, or small numbers in data cells).

The Breast Screening Select system provides information on trial entrants, including patient identifiers such as name, NHS number and date of birth, for record linkage. Participants' records are linked securely and electronically to:

– NHS screening records (for screening history and information about procedures done and diagnoses) at NHS England;

– Death and cancer registry data, including the Cancer Outcomes dataset, held by NHS England (previously Public Health England 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;

– NHS Hospital Episode Statistics, held by NHS England (formerly NHS Digital and Health and Social Care Information Centre)) for information on cause-specific hospital admissions and procedures, including surgical treatments such as mastectomy, lumpectomy, axillary clearance, etc; and

– Data approved for anonymised transfer from a nationwide prospective study with information on quality of life.

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, one in younger women and one in older women

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 invitations 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 analyses will be restricted to women who can be identified and followed up and for whom unbiased evidence (which cannot itself be altered by the random allocation) shows that allocation of whether or not to send a screening invitation is likely to determine whether or not the woman is actually screened.

These analyses will therefore 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 unbiased records to have moved away from the address held by the Breast Screening Select (formerly National Breast Screening) System; women known from unbiased records to have had cancer (except non-melanoma skin cancer), breast disease, or breast surgery; and women entered since mid-2016 who were not quite 71 at the time (Annex 1).

Of the remaining women, a proportion would not take up a screening invitation even if they were sent one, thereby diluting any effects of inviting women for screening. 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. (For, in older women a strong predictor of acceptance of an invitation for breast screening is previous attendance for breast screening at their last routine invitation. Likewise, in younger women previous attendance for routine cervical screening is a strong predictor of acceptance of a first invitation for breast screening.)[2]

Statistical power
Women aged 47-49: The median age of the women randomised in their late 40s will be 48 years. Among one million women during the 2010s with no breast cancer before age 48 who are randomly allocated not to have a screening invitation before age 51, 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 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 screening by the BSP or other providers 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 exclusions described above will somewhat increase this statistical power, as will longer follow-up (13).

[2] 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 (11). Likewise, survey data (12) 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.

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 only a small proportion will have more than 1 woman with a breast cancer diagnosed at or before routine screening began that causes death.

Women aged 71-73: Among one million women during the 2010s who had been screened at age 69 with no relevant abnormality detected, and who still had not been diagnosed with breast cancer by age 72, about 4000 might be expected to die of a subsequent breast cancer before age 80.

If an additional screen at age 72 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, women over 70 are already able to request screening every 3 years, and a minority already do this (4). With a more realistic uptake rate of 70% of those invited accepting the invitation and a realistic self-referral rate of about 10%, 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 exclusions described above will somewhat increase this statistical power, as will longer follow-up and additional screening invitations at ages 74-79.

Consent, confidentiality and trial supervision

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

Individual records will be linked to NHS England datasets, but will be anonymised once data linkage has been completed. The trial will be conducted in accordance with all relevant aspects of the requirements of CAG and the Data Protection Act. The data will be treated with appropriate confidentiality, and used only for medical research.

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 (DMEC)
The DMEC, 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. Its terms of reference 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[3] 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 (TMG)
The TMG 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 to 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.

ADAPTATION TO CHANGES IN ROUTINE BREAST SCREENING

During 2018, the NHS BSP improved its IT systems, adjusting which women would be invited for routine screening and hence adjusting which other women could therefore be invited into the AgeX trial (Annex 1). If, as may well be the case, further improvements in BSP software lead to any further adjustments in eligibility for routine screening, then these will automatically result in further adjustments to recruitment into the trial, to avoid any possibility of overlap in future years between eligibility for routine screening and eligibility for AgeX.

[3] 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.

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.

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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, Medical Director, St Georges Hospital, London (breast radiologist); Professor Alison Halliday, Nuffield Department of Surgery (surgeon, surgical trialist); Ms Jenny Rusby, Royal Marsden Hospital, London (consultant breast surgeon).

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Approvals and permissions Ethical approval in 2010, 2014, 2016 and 2018 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).

Website **www.AgeX.uk**

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

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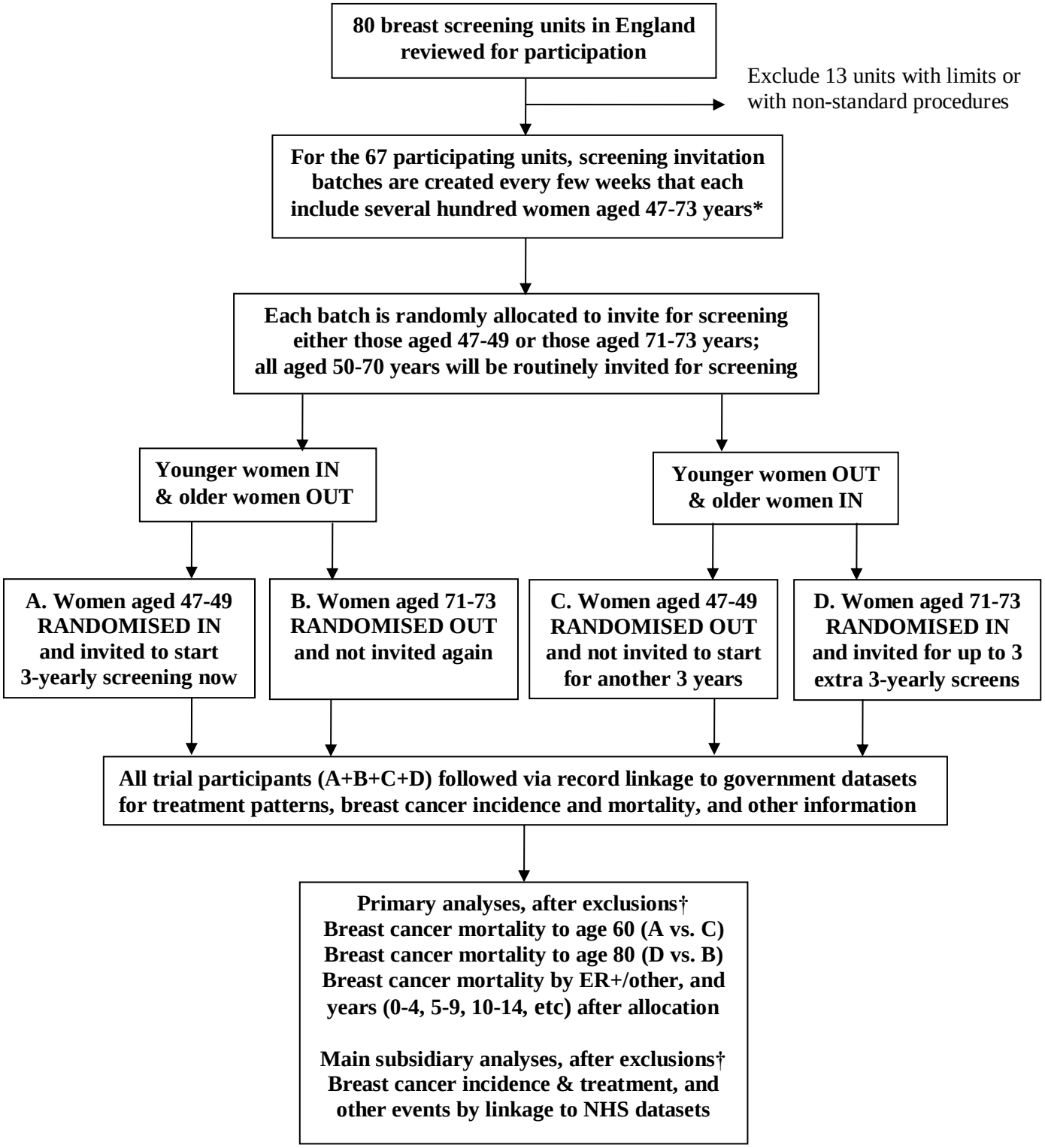
Figure: Flow diagram of randomisation, follow-up and principal analyses



* Details of how age is defined are given in Annex 3. The batch could also include trial participants invited 3 years ago at ages 71-73 (but now aged 74-76) for a second invitation and those invited 3years 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 for whom, from objective prior records, the randomised trial allocation is unlikely to affect whether or not they attend for screening (eg, those who had not taken up their previous screening invitation) – see text.

Annex 1: Effects of changing the details of the definition of the age range

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 extra 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 2: Information poster about the trial, 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 3: Patient information sheet (4 pages)

Available in other languages at www.AgeX.uk

The AgeX trial

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.

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 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 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

To order more copies of this leaflet visit: www.gov.uk/phe/screening-leaflets