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

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Summary

Background: The NHS 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, an England-wide cluster-randomised trial is under way. Its aim is to assess reliably the risks and benefits of additional invitations for screening before age 50 and, separately, 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 trial will involve about 71 of the 81 breast screening units in England and will randomise at least two million women aged 47-49 and one million aged 71-73 to be invited or not for additional screening. Women will be followed up by electronic linkage to NHS records to assess the short-term and long-term effects of the additional screening on: patterns of investigation, detection and treatment of breast lesions; breast cancer incidence; breast cancer mortality; hospital admissions; and overall mortality. The trial is registered, ISRCTN33292440 and NCT01081288.

Principal and subsidiary outcomes: The principal outcome for screening before age 50 and, separately, after age 70 will be breast cancer mortality, eventually subdivided by 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

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

Background

In 1987 a report commissioned by UK Health Ministers recommended that a mammographic screening programme be established in the UK (1). In 1988 the National Health Service Breast Screening Programme (NHSBSP) began, offering women aged 50-64 years triennial screening. In 2003 it was decided to extend the age range for screening from 50-64 to 50-70 years; proposals to randomise this age extension to obtain large-scale reliable information on both the risks and benefits of additional screening at ages 65-70 were not adopted. Another opportunity to obtain reliable evidence about the effects of extending the age range of routine screening arose in 2007, when the Prime Minister (Gordon Brown) announced further extension of the NHSBSP to 47-73 years (2). At that time insufficient funds were available for immediate roll-out of screening to all women aged 47-73, and a cluster-randomised trial of this age extension was proposed and agreed.

A pilot study to assess the feasibility and acceptability of cluster-randomisation of additional screening at ages 47-49 and 71-73 was conducted over a 12-month period from June 2009 in five breast screening units in England (3, 4). No major problems of feasibility or of acceptability of randomisation were found and in 2010 the main England-wide trial began, using the same randomisation procedure as in the pilot study.

When extension to ages 47-73 was announced in 2007, the intention was to offer breast cancer screening to all women in this age range after 2012 (2), but in 2011 the date was changed to 2016 at the earliest (5). Subsequently, Public Health England (now responsible for all screening programmes in England) stated that future decisions about extending routine NHS breast cancer screening outside the age range 50-70 years should await the emergence of reliable evidence as to its effects. The present trial can provide this.

Because of concerns about breast screening, the Department of Health and the charity Cancer Research UK set up an independent panel to review the evidence, in the context of the NHS screening programme (6). The panel reported in 2012 that "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 [ie, the present study] in the UK for randomising women under age 50 and above age 70 to be invited for breast screening."

The National Health Service Breast Screening Programme (NHSBSP)

The NHSBSP was the first nationwide population-based breast screening programme in the world. It began inviting women for screening in 1988, and full national coverage was achieved by the mid-1990s (7). During the past decade, free breast screening has been routinely offered every three years to women aged 50 to 70 years. Around 2.3 million women in this age range in England were invited for screening in the financial year 2012/13, with 1.7 million accepting (8). In England the Advisory Committee on Breast Cancer Screening oversees the programme and reports to government ministers (9). Currently, 81 breast screening units cover all of England, each responsible for a defined catchment area. The NHSBSP sets standards for the screening units and monitors performance through a national quality assurance network.

The Trial

Aim

The cluster-randomised Age Extension Trial will assess reliably the risks and benefits of offering an extra screening invitation to women aged 47-49 (who will be offered routine screening anyway by the NHSBSP 3 years later) and, separately, of offering additional screening to women aged over 70 (who will have already been offered routine triennial screening at ages 50-70 by the NHSBSP). Linkage with routinely collected NHS 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 nationwide NHS breast screening programme. Other than randomisation, all aspects of screening will be conducted exactly as normal in the NHSBSP, following all 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 71 of the 81 NHS breast screening units in England. The units expected not to participate are mainly those that use non-standard methods for creating screening batches (the unit of randomisation: see below). The five breast screening units that participated in the pilot study have become part of the main trial.

Trial entry by cluster random allocation of small batches

Randomisation is by cluster. As part of the routine breast screening programme, the NHS 'Exeter' computer system creates screening invitation batches, typically every few weeks, for each local breast screening unit. An invitation batch typically contains the contact details of several hundred women of appropriate age recorded (in the local 'Exeter' 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 unit to invite the women in it for screening.

Before the trial began, batches would have included women aged 50-70 years (by the end of the current year[1]). During the trial, batches include women aged 47-73 years rather than only those aged 50-70 years; 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, as it is being generated, 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 part of the trial).

[1] Age by end of the current year is 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 age range 49-52 (centred on 51.0) years.

The random allocation of each batch is done by a specially written computer programme with equal (50/50) probability and no stratification. For women in the batch who are to be invited for screening, invitations would generally be sent out within a few weeks of the batch being generated. New trial entrants in the batch who are randomly allocated not to be invited join the trial as controls. This was approved by the National Information Governance Board. 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.

Women aged 47-49 years in a batch where their age group is randomised not to be invited for screening can request to be screened, 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; nor was it widely taken up in the pilot study (4).

Number of trial participants
The total number of women entering the trial (half invited for additional screening and half not) will be at least 3 million (2 million in the 47-49 age group and 1 million in the 71-73 age group), but this 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 NHSBSP 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.

The National Breast Screening System provides information on the trial entrants that includes the patient identifiers needed for record linkage. Trial participants' records will be linked electronically to NHS screening records (for screening history and information about procedures done and diagnoses); to the NHS Central Register and the NHS Cancer Registry and 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 to NHS Hospital Episode Statistics (for information on cause-specific hospital admissions, including surgical treatments, such as mastectomy, lumpectomy, axillary clearance, etc).

Such routine records will cease when women are notified as emigrating, on which date their trial follow-up is censored, but this will probably affect fewer than 1% of the 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 hormone 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 an extra screening invitation among those who have had their final routine screening 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.

Main subsidiary analyses
The plausibility of the assumption of no other effects on 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
Women who on the exact date of randomisation had already died, were not living at the address held by the National Breast Screening System, or already had a record of pre-existing cancer or benign breast disease will be excluded from the primary and main subsidiary analyses. 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 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 the last routine invitation below that age. 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 cervical screening.[2]

Statistical power
Women aged 47-49: The median exact age of the women randomised in their late 40s will be 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 an uptake rate of only two-thirds, the expected difference would be only about 150 (with standard error 54, $p<0.01$), and about 80% chance of achieving $p<0.05$.

[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 (8). Likewise, survey data (10) 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.

Improved compliance would increase statistical power, as would longer follow-up (11). Intra-cluster correlation has little impact on these 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 that causes death and that was diagnosed before routine screening began.

Women aged 71-73: Among 0.5 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 2000 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 1700 deaths, then an evenly randomised trial among 1 million such women of an additional invitation, with 80% uptake, would reliably detect the expected difference of 240 relevant deaths (with standard error 61), yielding about a 91% chance of achieving a $p<0.01$ result. Again, longer follow-up would increase statistical power.

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. The NHSBSP 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 other NHS 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 their 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 journals, 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 ages 47-49 years or at ages 71-73 years 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 any reasonable doubt[3] that an additional screening invitation at ages 47-49 years or at ages 71-73 years will reduce breast cancer mortality by age 60 or by age 80 respectively 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.

Trial participant information sheet
Women invited for screening under the NHS Breast Screening Programme receive with their screening invitation the standard NHSBSP breast screening 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 NHSBSP patient brochure is current, together with the trial participant information sheet (Annex).

[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.

Approvals and permissions Ethical approval in 2010 was from Ealing & West London 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 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).
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Investigators Professor Julietta Patnick, director of NHS Cancer Screening Programmes (principal investigator); Professor Dame Valerie Beral, director of Cancer Epidemiology Unit, University of Oxford; Kath Moser (trial coordinator), Cancer Epidemiology Unit, University of Oxford; Professor Sir Richard Peto, co-director of Clinical Trial Service Unit, University of Oxford; Professor Sir Mike Richards, chief inspector of hospitals and formerly National Cancer Director.

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); [redacted]; Ms Jenny Rusby, Royal Marsden Hospital, London (consultant breast surgeon).

Trial Management Group Professor Julietta Patnick (chair), director of NHS Breast Screening Programme (principal investigator); Professor Dame Valerie Beral, director of Cancer Epidemiology Unit, University of Oxford (epidemiologist, co-investigator, Chair, 2001-11, of the Advisory Committee on Breast Cancer Screening); Lucy Carpenter (lay member); Kevin Fenton, director of Health and Wellbeing, Public Health England (public health epidemiologist); Kath Moser, Cancer Epidemiology Unit, University of Oxford (demographer, trial co-ordinator, co-investigator); Dr Hongchao Pan, Clinical Trial Service Unit, University of Oxford (statistician); Professor Sir Richard Peto, co-director of Clinical Trial Service Unit, University of Oxford (statistician, specialist in large-scale randomised evidence, co-investigator); [redacted]; Professor Sir Mike Richards, chief inspector of hospitals and formerly National Cancer Director (co-investigator); [redacted] Margot Wheaton, former chair of the NHSBSP General Administration and IT coordinating group and programme manager of the Warwickshire, Solihull & Coventry Breast Screening Service; [redacted].

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Participating breast screening units (current and expected)
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; Kent & Canterbury; Maidstone; Medway.

Annex: Trial participant information leaflet

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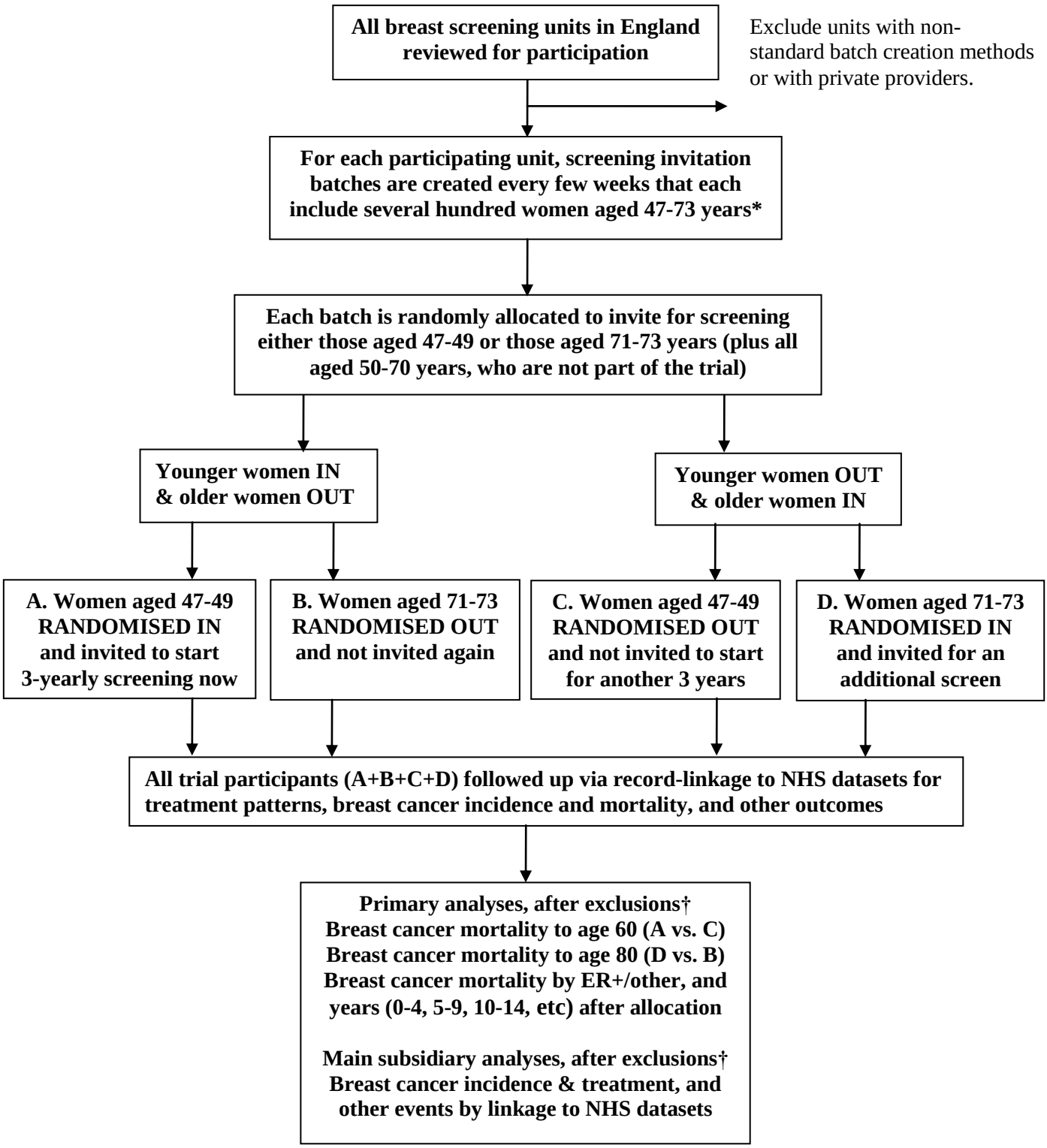
Figure: Flow diagram of randomisation, follow-up and principal analyses



* In this flow diagram, age means age by the end of the current calendar year.
† Exclude from these analyses, and report separately, various relatively uninformative categories of women (e.g. those who prior to random allocation had already died, had a record of prior cancer or breast disease, had moved from catchment area, had not taken up their previous screening invitation, etc – see text).