

ANALYSIS

Cost of extending the NHS breast screening age range in England

Susan Bewley and colleagues examine the clinical and ethical implications of Public Health England's trial of widening the age limits for breast cancer screening

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AgeX is the acronym for the UK government inspired and funded, cluster randomised controlled trial of extending the NHS breast cancer screening age range in England. The trial aims to assess the risks and benefits of extending mammography screening for breast cancer outside the current 50-70 year age range by offering one extra mammogram to women between the ages of 47 and 49 and up to three to those over 70. Announced as "likely to be the largest randomised controlled trial ever undertaken in the world,"¹ during 2010-16 AgeX randomised three million women into the extended age groups and screened one million.²

Concerns have been raised over the adequacy of information on benefits and risks provided to women in the study, which carries risk of surgical and other harms to participants. Women learn of their inclusion in research through a letter with a prebooked screening appointment. We highlight the likely surgical burden for women aged 47-49 and consider whether extending breast screening is still appropriate as accumulating evidence challenges its assumed benefits.

Breast screening policy and controversy

Mammography screening aims to find breast cancer before a lump is palpable, giving the opportunity to start treatment earlier.³ The current UK screening programme, started in 1988, offers triennial mammography to all women aged 50-70. Of the 2.85 million women invited in 2015-16, 75% attended. In common with programmes worldwide, the screening age range was defined based on evidence of when mammography is most effective at detecting tumours in the breast.

The programme has been estimated to prevent 1300 deaths from breast cancer each year.⁴ But evidence suggests improvements

in breast cancer survival rates since the introduction of mass screening probably result from concurrent improvements in the adjuvant hormonal and chemotherapy used to treat breast cancer.^{5,6} There is also evidence that screening does not reduce the number of tumours reaching late stage and that it results in substantial overdiagnosis,⁷ with consequent radiotherapy, lumpectomies, and mastectomies.

Age extension trial

In 2007 the Labour government's cancer reform strategy recognised late diagnosis as a factor contributing to poor cancer survival rates in the UK.⁸ It seemed logical to assume that the earliest diagnosis would offer the greatest chance of cure, so the government's proposals included extending the age range for breast cancer screening. By 2012, it promised, women would receive nine screens between the ages of 47 and 73, with a guaranteed first mammogram before age 50. Limited capacity forced a decision to phase in the proposed extension. According to the organisers, randomising would, "provide a unique opportunity to obtain unbiased evidence on the net effects of the new policy," although the extension would "proceed regardless of whether the study goes ahead or not" (see appendix 1 on bmj.com).

The Nationwide Randomised Trial of Extending the NHS Breast Screening Age Range was started by Public Health England in June 2009 with an original expected participation of 1.1 million women over 13 years. The cluster design randomises batches of 1000 screening invitations normally sent to women aged 50-70 to be extended to comprise those aged either 47-70 or 50-73. Half of all women aged 47-49 and half of all women aged 71-73 are invited to screening, while all women aged 50-70

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Data supplements on bmj.com (see <http://www.bmj.com/content/364/bmj.l1293?tab=related#datasupp>)

Timeline of AgeX trial

Appendix 1: First version of trial protocol

Appendix 2: Table showing changes to protocol

are invited to screening as usual. The trial compares breast cancer incidence and mortality between screened and unscreened participants in the studied population. In 2016, the Age Extension trial was renamed as AgeX. The recruitment target was raised to “at least six million.”⁹

Shaky foundation

It is laudable to test government policy before it is rolled out. But the design of this trial does not meet standards for generating evidence that would be robust enough to inform future policy, as described below.

Evidence base—It is good practice for scientific experiments to be preceded by a systematic review of the evidence to avoid wasteful research and repeating unnecessary harms. Here, there was no such review. Emerging concerns about the lack of efficacy and potential harms of screening were mentioned briefly as “so-called overdiagnosis” in AgeX’s seven page original trial protocol (appendix 1). The trial’s sponsor (University of Oxford), when asked whether the protocol had been subjected to independent scientific peer review, told us only that it had been reviewed by the Department of Health advisory committee on breast cancer screening.

Outcomes—AgeX’s primary outcome measure is death from breast cancer. Total cancer deaths are not recorded, and overall mortality was added in 2016 as a subsidiary outcome but will not be included in the primary analysis. Measuring breast cancer mortality alone excludes deaths resulting from side effects of treatment or cancers caused by mammography. This is relevant as suitably randomised trials of breast cancer screening find no effect on total cancer mortality.³

Potential for bias—Estimates of breast cancer mortality in screening are particularly vulnerable to bias because large numbers need to be screened to see the small effect and there is a long lead time for outcomes to become evident. Bias in suboptimally randomised trials of breast cancer screening may have resulted in benefit being overestimated.¹⁰ During the past decade, AgeX increased its planned duration and sample size, study outcomes were changed, and a proposal for statistical analysis was retrospectively appended (appendix 2 on bmj.com). These factors, coupled with the protocol’s stated plan to continue the trial beyond a “fixed, predetermined sample size” until “clear answers emerge” all increase the likelihood of a biased assessment.

Lack of explicit, fully informed consent

According to good clinical practice, trial participants must be told that they are in a trial and given details of all known benefits and harms in language they can understand.

When the age extension trial was first conceived, screening was already known to be associated with harms, but these were not believed to outweigh the benefits of early detection. Harms range from false positive results with associated psychological distress to overdiagnosis—with abnormalities that would not have harmed the woman in her lifetime being found, leading to potentially dangerous, painful, and disfiguring treatment.

Early AgeX trial documentation refers to “so-called overdiagnosis” (appendix 1). But the team’s assumption that overdiagnosis was unimportant was challenged in 2012 when the Independent UK Panel on Breast Cancer Screening, chaired by Michael Marmot, published a detailed review of the evidence. The report recognised and quantified overdiagnosis—for every breast cancer death averted, three “cancers” that would never have troubled women during their lifetimes would be found and

treated.⁴ The physical and psychological harms resulting from such treatment are substantial. Yet in 2016, when AgeX’s recruitment target was raised to six million, this increase—with corresponding potential for harm—was not referred to or justified in an accompanying application for ethics approval.

With Marmot’s publication, the confirmation that predicted benefits were accompanied by appreciable and quantifiable risks to participants should have triggered a reflective review of the research question and study design. Crucially, this should have included whether participants should now be given full risk-benefit information and the opportunity for explicit, fully informed consent.

In AgeX, an early decision had been taken to forgo such consent. The original protocol said, “100% coverage is essential for the scientific validity of the study, and excluding participants for whom we cannot get consent could seriously bias the results ... consent is implied for those who attend for screening.” Women in the invited clusters learn of their inclusion through a letter with a prebooked screening appointment, general mammography advisory notes with the sign-off, “Remember ... screening saves lives,” a brief leaflet describing the trial (but not the potential risks of participation), and the standard pink breast cancer screening booklet written for women aged 50-70.¹¹ The trial participation leaflet was expanded in 2014 from one to four pages,¹² but description of risk is limited to “be[ing] asked to return for more tests.” Trial participants’ understanding that they are voluntary participants in research rather than routine NHS screening, and at risk of unnecessary surgery and other harms, is never explicitly checked.

Cluster randomised trials can be run without seeking individual participants’ explicit, fully informed consent. As participants are randomised in large groups to invitation batches for a local breast screening unit, obtaining prior consent from individuals in the cluster is normally unfeasible.

International guidance on the conduct of such cluster randomised trials states that the requirement for consent may be waived when the study intervention(s) poses no more than minimal risk.¹³ We believe that the level of risk to participants in AgeX necessitates a trial design that enables fully informed consent.

The public overestimates the benefits and has a poor sense of the harms of screening tests in general,¹⁴⁻¹⁷ so researchers have a responsibility to dispel misconceptions. Physicians themselves often do not fully understand the benefit:harm ratios and consequently are poorly equipped to counsel their patients.^{15 18 19} Well designed decision aids²⁰ could support doctors and their patients, but AgeX does not refer to any.

Our complaint to AgeX’s principal investigator about the paucity of participant information was rebutted by saying the approach had been approved by ethics committee. A similar complaint to the ethics committee was in turn responded to by deferring to the principal investigator’s assurances.

Effects of extending age range

Information about the balance of risks and harms may be particularly relevant for women over 70. The risk of developing breast cancer increases with age. In 2014 a prospective nationwide population based study of breast cancer screening in women aged 69-75 in the Netherlands reported a steep rise in the numbers of “early” cancers in the screened group, without significantly reducing numbers of advanced cancer cases.²¹ Effectively, screening was leading to many more older women “living with cancer,” with little effect on actual deaths from breast cancer.

Although such observational evidence may not be as powerful as that from a randomised trial, a study of this size should have flashed a warning light. Instead, in 2016 AgeX was amended to further extend the programme for older women, who would now be invited triennially at ages 71-76, or 71-79 subject to funding.⁹

Older women are less able to tolerate surgery than younger women because of increased likelihood of comorbidities,²² so overdiagnosis and overtreatment have a greater effect on their quality of life and physical function. This information should be made available to women considering screening.

We cannot yet know the full effects—good and bad—of extending the age range for breast cancer screening, but a study from Devon, southwest England, sheds light on one aspect: the numbers of extra surgical procedures in the younger women screened.²³ In Devon, all women aged 47-49 are invited for screening because Inhealth, the region's breast cancer screening provider, is not permitted to take part in clinical trials. The results from the first year show that 4250 (76%) of the 5624 invited women in this age group were screened, resulting in 125 surgical outpatient consultations and 53 operations. This gives an indication of the short term extra surgical workload from screening women under 50, although as the study authors point out, estimating the longer term surgical and financial effect is more complex.

Women participating in the AgeX trial must be given the opportunity to balance the possibility of lesions being detected earlier (with more opportunity for breast conserving surgery) against real risks of harm. Extrapolating the Devon figures to all women in England screened before age 50 over the duration of AgeX, we estimate that several thousand women would need surgery. Given what we know about overdiagnosis in breast cancer screening from sources such as the Independent UK Panel on Breast Cancer screening⁴, we know that a substantial proportion of this surgery will be unnecessary. The full financial and human costs of AgeX will also include extra general practitioner visits and physical and psychological harms from diagnoses of cancer that otherwise would not have caused problems during the women's lifetime. The trauma of living with cancer can be lifelong, including lasting effects of surgery or other treatments, fear of recurrence, and loss of self esteem and body confidence. Research shows that when women are fully informed of the risks and benefits of regular screening, fewer opt to be screened.²⁴

Despite pressures on NHS budgets, AgeX increases the workload for the already stretched NHS breast screening programme by 14%.²⁵ The resulting extra treatment also creates a considerable burden on the NHS.

Conclusion

The balance of benefits and harms from breast cancer screening remains contested. Three years after AgeX began, an architect of the NHS breast cancer screening programmes argued that deaths after treatment of screen diagnosed breast cancer may exceed those from breast cancer in an unscreened population.²⁶ In 2014, the Swiss medical board advised its government to stop recommending mammography screening.²⁷ In 2016, an open letter from French scientists who had conducted a consultation into France's breast cancer screening for their ministry for health called for a halt to breast cancer screening for low risk women under 50, and an end or thorough review of the programme for women over 50.²⁸

People must be given sufficient information to decide whether they wish to participate in research, particularly when the risks

are unclear. We recommend the National Screening Committee uses high quality fact boxes and icon arrays²⁰ to support patient consent in AgeX and all screening programmes. We call on the investigators and verifiers of any data resulting from AgeX to use all-cause death as the primary outcome. An independent inquiry into the scientific quality, governance arrangements, and ethical issues arising from the trial would inform future high standards for the design and conduct of government run trials.

Key messages

Public Health England began recruiting millions of women to the Age Extension Trial of Breast Cancer Screening in 2009, before of harms of overdiagnosis were fully recognised

The cluster randomised trial is criticised for its design, conduct, and lack of transparent scientific processes

The resulting evidence may therefore not be robust enough to inform policy

Participants' understanding and consent to participate in research are not checked despite the risks of surgical and psychological harm

We thank the UK charity HealthWatch and Les Rose, retired clinical research consultant, for his help and advice throughout our investigations.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following: SB and MB are members of the UK charity HealthWatch 'for science and integrity in healthcare' and of a breast cancer screening Google group. MP is editor of the HealthWatch newsletter and a freelance medical publications consultant. SB and MP have declined screening mammography. MB is a lay reviewer for *The BMJ* and declined an invitation to breast screening as part of the Age Extension Clinical Trial pilot.

Contributors and sources: SB conceived and prepared the analysis and first draft. MP contributed to reviewing literature, data analysis, and writing final draft. All authors contributed, critically reviewed the manuscript, and approved the final version. SB acts as guarantor.

Patient participation: MB is a former breast cancer patient, a BMJ patient reviewer, and first raised concerns with the Harrow ethics committee's decision to approve the trial.

Provenance and peer review: Not commissioned; externally peer reviewed.

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