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Alpha House, University of Southampton Science Park
Southampton SO16 7NS
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PROTOCOL FOR LONG TERM FOLLOW-UP OF A TRIAL TO STUDY THE EFFECT OF ROUTINE MAMMOGRAPHIC SCREENING STARTING AT AGE 40 ON BREAST CANCER MORTALITY (ISRCTN 24647151)

(September 2011)

Background

The incidence of breast cancer increases with increasing age; however there were over 5500 breast cancer registrations at ages 40-49 in England in 2007, and over 1400 deaths at ages 40-54. Breast cancer is the most common cause of death from cancer in women at ages 35-54. Survival from breast cancer is improved by earlier diagnosis, and population screening has been shown to be effective in reducing mortality from the disease in women over the age of 50. The breast screening programme in England, which invites women from age 50 (now being lowered to age 47), is estimated to save around 1,250 lives a year. The effectiveness of screening for breast cancer by mammography in women below age 50 remains less clear, and continues to be the subject of much debate. Despite lower mortality from the disease at younger ages, the issue is an important public health question in this country, due both to the demands of the women concerned and the possible implications for the NHS. Screening between the ages of 40 and 50 has the potential to reduce mortality from breast cancer up to at least age 60.

Existing research: Combined evidence from a number of randomised controlled trials increasingly suggests the existence of some benefit from screening in women below age 50 at trial entry[1]; in settings where mammography screening below age 50 has been undertaken on a population basis, there is also some evidence of effectiveness in terms of mortality reduction[2 3].

However, none of these previous trials was specifically designed to address this question, and the extent to which observed benefit results from screening in these women after they reach age 50 remains unclear.

The AGE trial is the only randomised controlled trial to have been conducted looking specifically at the effect of mammographic screening from age 40 on breast cancer mortality, The first mortality results, based on an average of 10 years follow-up, showed a non-significant 17% reduction in breast cancer mortality in women offered screening[4], equivalent to a reduction in absolute risk of 0.40 per 1000 women invited, but the full effect of screening in the trial is not likely to have emerged at this time.

The question of the relative benefits and harms of mammographic screening in women below age 50 remains a controversial area. A meta-analysis has found that whilst the relative risk reductions in women aged 50 to 59 years and 40 to 49 years were similar (14% and 15% respectively), the absolute risk reduction was greater for women aged 50 to 59 years, leading to a number needed to invite for screening (NNS) of 1339 in women aged 50 to 59 compared to 1904 for the younger age group[1]. The AGE trial is the most recent of these trials, and the only one in which all women entered at age 40 years.

The number of women needed to be invited (NNS) in the AGE trial for 7.9 years to prevent one death from breast cancer over 10 years has been estimated as 2512[4]. However the NNS is dependent on both length of intervention and length of follow up, and longer follow up will permit an estimate more comparable with those available from other trials.

The potential harms of screening include the risk of false positive mammograms, and possible resulting anxiety. An analysis of the AGE trial has found a cumulative risk over 7 annual screens of 20.5%[5], the false positive rates being similar to those in older women, but with a lower positive predictive value of referral for cancer due to the lower cancer detection rate. However, women with previous false positive mammograms were no less likely to attend for subsequent screening. We have also conducted a detailed pathology review of all breast cancer cases diagnosed in the trial up to the first NHSBSP screen[6], and have conducted a study showing that screening in the control arm during the course of the trial was limited [7].

Plan of Investigation

The trial protocol is summarised in Figure 1. The trial includes 160,000 women, randomised in the ratio 1:2 to an intervention arm and control arm. Individual randomisation was performed, but stratified by GP practice so that one-third of the women in any practice were allocated to the intervention arm. Women were aged 39-41 years at time of entry to the trial, and recruitment took place between 1991 and 1996. The trial has been conducted in 23 NHSBSP breast screening units in England, Wales and Scotland. Women in the intervention arm were sent a letter of invitation, together with an information leaflet, stating clearly that the woman is being asked to participate in a research trial, and her acceptance of the invitation is taken to be her informed consent to participate. Women in the intervention arm were invited for annual mammographic screening until the calendar year of their 48th birthday. After age 50 both they and women in the control arm become eligible for invitation three yearly as part of the NHSBSP, and will receive their first invitation between age 50 and 52. Screening in the trial was by two-view mammography at the first screen, with single view thereafter unless otherwise indicated. All women, including non-attenders, were re-invited annually unless they requested otherwise. Women who moved to areas not covered by the trial were not re-invited for screening as part of the trial, but were able to self-refer to either their previous or their nearest participating screening centre. Screening in three centres ceased prematurely (after four, five and six rounds respectively) due to the inability of the centres to manage the additional workload within the available resources.

The trial database contains information on all screening as part of the trial in women in the intervention arm of the trial. It also contains data on the first screening invitation and attendance at ages 50-52 years as part of the national screening programme in women in both the intervention and control arms. The latter data have been collected not only from the 23 centres participating in the trial, but from all NHSBSP screening units in England, Wales and Scotland, providing information on screening in women who have moved away from their original trial centre. Data on this first NHSBSP screen are estimated to be 93% complete, with similar percentages in the two trial arms. Information on screening includes attendance, outcome of initial mammogram (i.e. whether the woman was recalled for further assessment) and final outcome of the screening episode.

The data recorded on trial women on the screening centre system are identical to those collected for women in the national programme. Detailed pathological information has been obtained on breast cancer cases diagnosed up to the time of each woman's first screen as part of the NHSBSP, and a pathology review conducted.

The primary outcome measure of the trial is mortality from breast cancer. Based on results from the earlier UK Trial of Early Detection of Breast Cancer[8], it was decided from the outset of the trial to use underlying cause of death from the death certificate rather than undertake a verification exercise. All women in this trial have been flagged at the NHS central register (NHSCR), now controlled by the NHS Information Centre, and more than 99.9% successfully traced. This provides data on all cancer registrations and deaths, including data on underlying coded cause of death, and also on emigrations. The majority of these data are now supplied electronically, with the exception of data from Scotland. Data obtained from the Information Centre will continued to be added to this central trial database. Data will continue to be accrued on cancers and deaths occurring until the end of 2017, at which time all women in the trial will have reached the age of 60 years.

Planned analyses

Planned analyses include mortality analyses including data to the end of 2010, when follow-up in the trial will be an average of 16 years (ranging from 13 to 20 years). Analyses will also be conducted with longer follow up periods, specifically on data to the end of 2017, when all women will have reached age 60. Analyses will compare the cumulative mortality from breast cancer in control and intervention arms ('intention to screen' analysis), over the total follow up and in years 1-5, 0-10, 10-16 etc, and the absolute reduction in breast cancer mortality in the intervention arm compared with the control arm; to allow updated estimates to be made of the number need to be invited for screening (NNS), and the number needed to be screened (NNBS) to prevent one death from breast cancer.

Analyses will also be restricted to breast cancer deaths occurring in cases diagnosed prior to each woman's first NHSBSP screen, and/or to age 49. At the point when all women have been invited to their first NHSBSP screen, breast cancer incidence in the control arm should have 'caught up' with that in the intervention arm, allowing the effect of screening in the trial alone to be estimated[9]. However the possibility of some over-diagnosis due to screening in the trial remains, and other methods for adjusting for the dilution effect, will be explored.

Analyses will also be conducted to estimate the effect of screening in those women attending for screening ('per protocol' analysis). This will use an established method [10] to adjust for selection bias, which arises due to the fact that non-attenders for screening are likely to be at different level of risk of breast cancer mortality than those attending.

Analyses of all cause mortality and of the major causes of death will be conducted to determine any observable bias. Analyses of excess mortality [11], in which the case fatality in breast cancer cases in the control arm is used to estimate the reduction in mortality in the intervention arm will also be performed.

Analyses of the cumulative incidence of breast cancer by trial from date of trial entry will be conducted at the time of each mortality analysis. Such analyses will estimate the extent of additional over-diagnosis in the intervention arm resulting from screening at age 50. The cumulative incidence of both in situ and invasive breast cancer will be compared between trial arms.

Statistical power

The trial was designed to have 80% power to detect a 20% reduction in breast cancer mortality over 10 years, at the 5% significance level and using a 1-tailed test. The estimated sample size was calculated as 130,000 in the control arm and 65,000 in the intervention arm. This was based on an estimated breast cancer mortality of 3.3 per 1000 over 10 years in the control arm in an initially disease free population. A reduction of 20% in the intervention arm as a whole with 70% compliance is equivalent to a reduction of 29% in those accepting screening (assuming no selection bias).

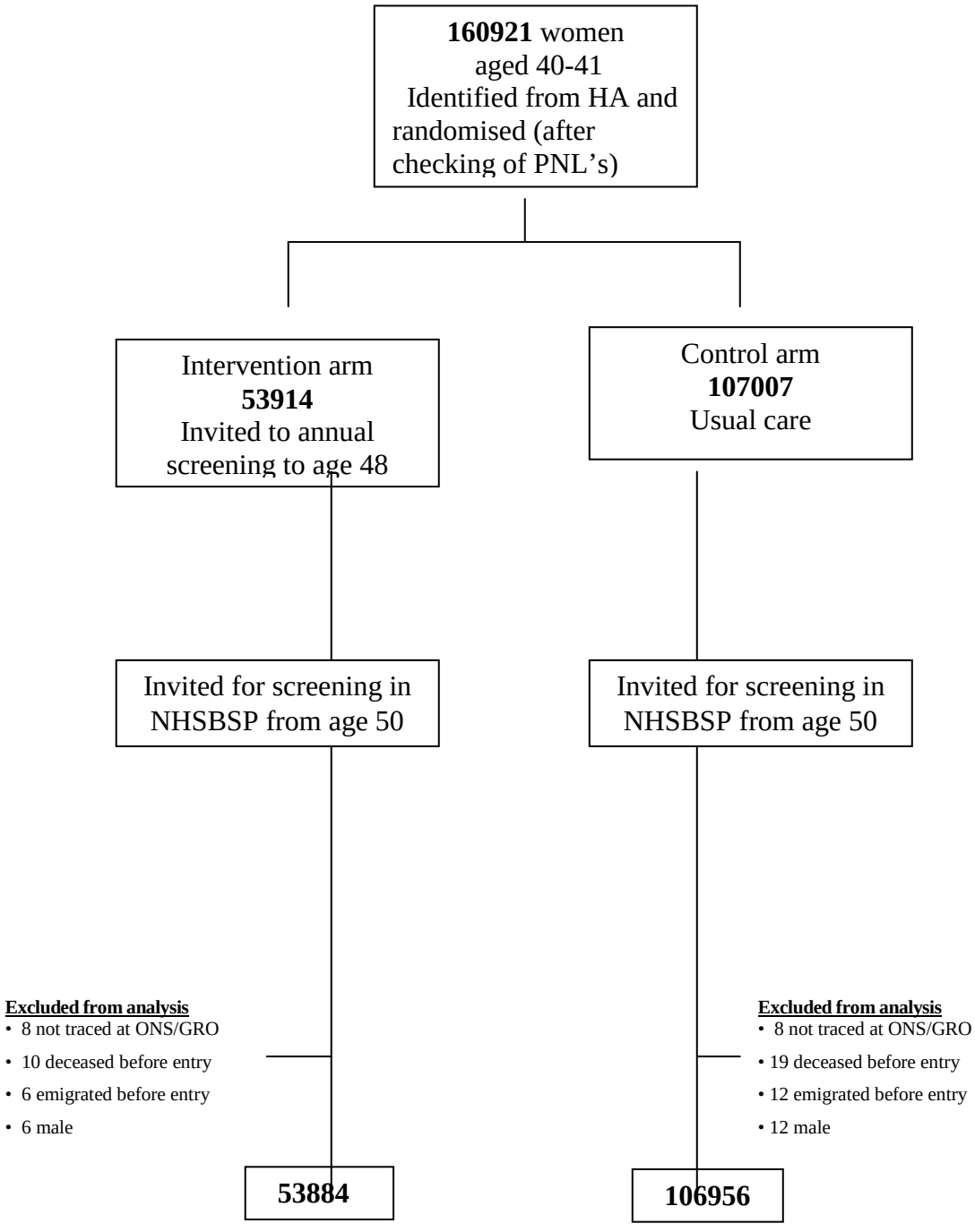
It was subsequently agreed by the Trial Steering Committee that recruitment to the trial should stop with 160,000 women randomised. The DMC considered the effect of this reduced sample size in September 1999, and concluded that the current numbers provided an acceptable sample size for completion of the study, and retained 79% power to detect a (plausible) 24% mortality reduction.

An analysis of breast cancer mortality based on data to December 2010 would have >85% power to show a 20% reduction in the intervention arm, assuming a cumulative mortality rate in the control arm of at least 6 per 1000 women**.** The analysis to 2017 would have > 80% power to show a 17% reduction, with a cumulative mortality rate in the control group of at least 8 per 1000 women.

Ethics and research governance

The trial has approval from London MREC (MREC/98/2/40). We have NIGB (formerly PIAG) approval (reference no 3-07(h)/2002) to hold identifiable information on all trial women, and to obtain pathology reports and slides for breast cancer cases without informed consent, which would be impractical to obtain given the size of the trial population, and the fact that two-thirds of the women are in the control arm and are unaware of their inclusion. (When the trial was designed and awarded ethics approval it was considered acceptable to have an uninvited control group who were unaware of their involvement in the trial, on the basis that such a group is no different to a geographically distinct population, who are followed up in order to monitor cancer incidence and mortality, and who are receiving the usual 'standard of care' for the general population).

Figure 1 Flow diagram of the progress through the phases of the trial



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