Mammo-50

PROTOCOL

Mammographic surveillance in breast cancer patients aged 50 years or older

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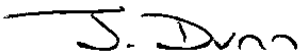

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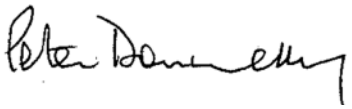

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ABBREVIATIONS

Abbreviation	Explanation
ACS	Assessment of survivor concerns
CI	Chief Investigator
CHI	Community Health Index
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSG	Clinical Studies Group
CT	Computerised Tomography
DCIS	Ductal Carcinoma In-situ
DSS	Disease Specific Survival
DT	Distress thermometer
EDC	Electronic data capture
ER	Oestrogen Receptor
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episodes Statistics
HSCIC	Health & Social Care Information Centre
HTA	NIHR Health Technology Assessment
IBTR	Ipsilateral breast tumour recurrences
ICH	International Conference on Harmonisation
ICPV	Independent cancer patients voice
IDMEC	Independent Data Monitoring and Ethics Committee
QSS	Qualitative Sub-Study
Main REC	Main Research Ethics Committee
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCIN	National Cancer Intelligence Network
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NICE	National Institute for Clinical Excellence
NPI	Nottingham Prognostic Index
ONS	Office of National Statistics
PHE	Public Health England
PPI	Patient and Public Involvement
QA	Quality assurance
QoL	Quality of Life
RCT	Randomised controlled trial
R&D	Research and Development
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry and Warwickshire
WCTU	Warwick Clinical Trials Unit

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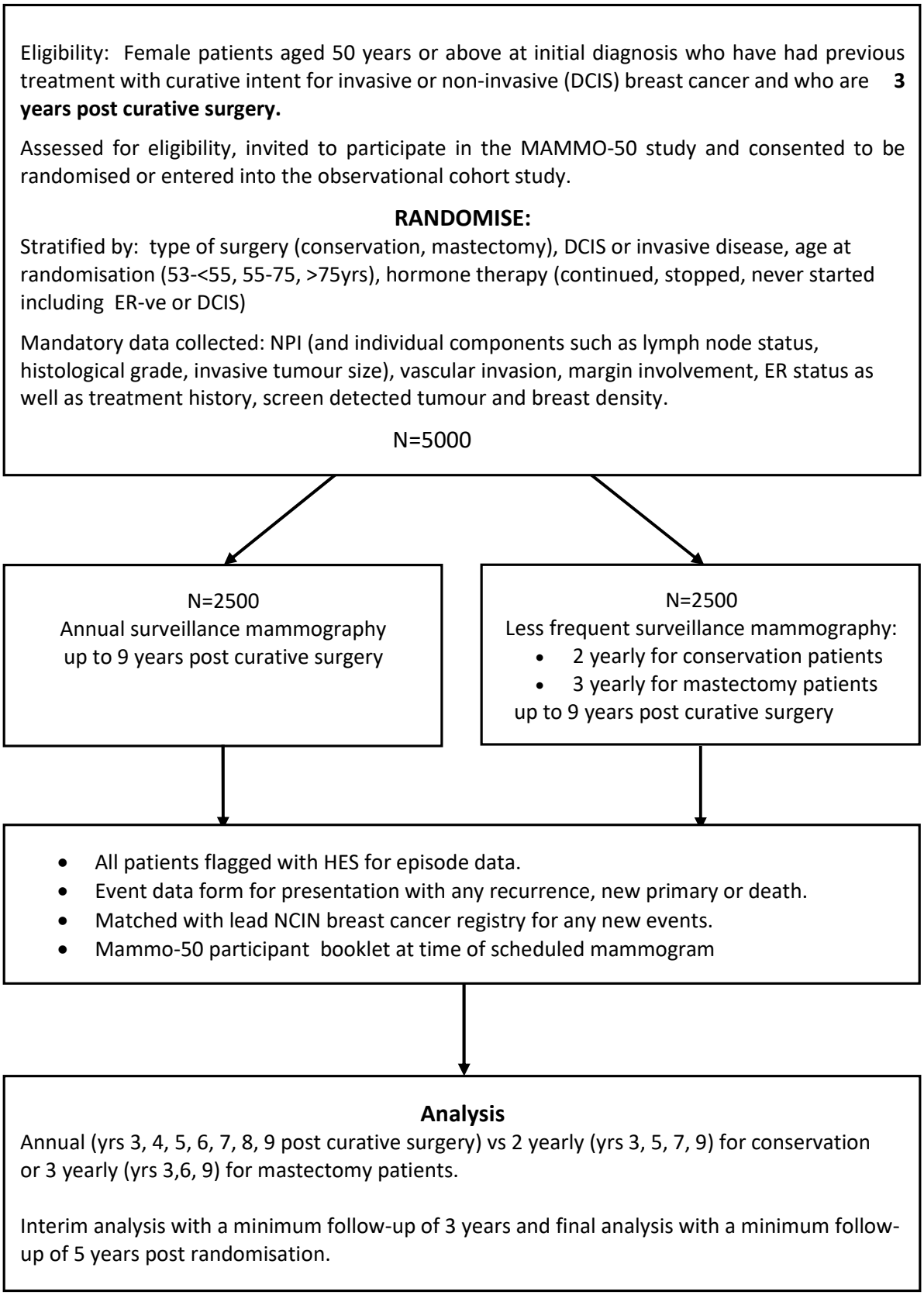
1. Trial Summary

Title:	**Mammographic surveillance in breast cancer patients aged 50 years or older**
Rationale:	The Government`s Cancer Reform Strategy recommends breast cancer patients be supported in self-care and have personalised risk-adjusted follow-up to meet their needs. As young age is a strong predictor of invasive and non-invasive "second" breast cancer (i.e. recurrence on treated side or new cancer in opposite breast), current NICE 2009 guidance recommends patients diagnosed up to 50 years have mammograms annually. For those patients aged 50 or older at diagnosis, there is no clear evidence or consensus amongst specialists on risk-factors to advise the optimum frequency or duration of follow-up mammograms. Type of breast surgery (mastectomy or conservation) does not affect long term survival. However, 3 years after diagnosis, second breast cancers are found less frequently by mammography in mastectomy patients than those patients who have had conservation surgery. Early detection of second cancers or metastasis is more likely to occur via patient self-examination between mammograms than by specialist clinic visit. A patient's ability to self-check and report concerns could be improved by alternative follow-up regimens including questionnaires and/or contact with nurses GPs, radiographers or internet access. There have been no randomised controlled trials in this setting. In order to provide sound evidence for future management, this clinical trial aims to establish if patients aged 50 years or over can be identified, who require less frequent mammographic surveillance whilst investigating alternative methods of follow-up.
Trial Design:	A multi-centre, randomised, controlled, phase III trial of annual mammography versus 2 yearly for conservation surgery patients and 3 yearly for mastectomy patients. There will also be an observational cohort study of those eligible patients for whom the specialist or patient opts for continued mammography per local practice or immediate discharge to the screening programme or stopping altogether. Randomisation will be stratified by type of surgery (conservation, mastectomy), DCIS or invasive disease, age at randomisation (53-<55, 55-75, >75 yrs), hormone therapy at randomisation (continued, stopped, never started (including ER-ve or DCIS). In addition mandatory information on known risk factors for recurrence/new primaries such as margin involvement, lymph node status, vascular invasion, histological grade, invasive size, ER status as well as treatment history, and breast density will be collected.
Setting	Breast cancer centres/units in the United Kingdom
No. of patients	Main trial: 5000 patients; Observational cohort: up to 2000 patients
Population	Female patients previously treated surgically with curative intent for invasive or non-invasive (DCIS) breast cancer in breast cancer centres/units in the UK. Patients will be 50 years or over at initial diagnosis and 3 years post-surgery, undergoing surveillance mammography.

Outcomes:	**Primary outcomes:** 1. Disease specific survival 2. Cost effectiveness **Secondary outcomes:** 1. Recurrence (time to recurrence, type of recurrence and features of recurrence plus new primary in ipsilateral breast and new primary in contralateral breast) 2. Number of referrals back to the hospital system 3. Long term survival (20 years post-surgery) **Outcomes for sub-studies:** 4. Quality of Life 5. Qualitative interviews assessing: a. Experience with the support provided for rapid assessment of new symptoms b. Experience with follow-up strategies assessed by patient, specialist, breast nurse & GP 6. Pathology assessing biomarkers at relapse
Sample size:	Assuming that patients who have survived and are recurrence free at 3 years post-surgery have a 5 year disease specific survival for the next 5 years of 89%, then randomising 5000 patients (2500 per arm) will allow detection of non-inferiority with a 2.5% 1-sided significance and 90% power, defining non-inferiority as no worse than 3% below the standard arm. A Quality of Life sub-study of at least 600 patients would be sufficient to detect a relatively small standardised difference of 0.3 with 90% power and 5% 2-sided significance level. For example, this would equate to a 7.5 change in quality of life assuming a conservative standard deviation of 25.
Project timetable	The first 6 months will see the set-up of at least 30 centres with randomisation of the first patient by January 2014. Recruitment of 5000 patients will be over the next 60 months given that 100 centres in total will be randomising within the first 18 months. An interim analysis will be performed after a minimum of 3 years follow-up for all patients. The final analysis of 5-year disease specific survival will be performed after a minimum of 5 years follow-up for all patients.

2. MAMMO-50 Flow diagram



3. Background

Much of what is known about the benefits and side effects of breast cancer treatment has been learnt from follow-up appointments in clinic. Current methods of follow-up involving clinical examination by a specialist in addition to mammography are costly, time-consuming and stressful if carried out long after diagnosis. Given that breast cancer is becoming more common with around 45,000 new cases diagnosed annually in the UK and survival is improving, the cost of follow-up represents a significant and increasing burden for the NHS (Cancer Research UK 2010). Alternative innovative methods of demonstrating that our patients are getting the best possible results from new treatments, with the least side effects, both short and long term, is the focus of this study and the goal of National Commissioning groups.

The Government's 2007 Cancer Reform Strategy and implementation plan 2009 recommends that patients be supported in self-care and have a personalised follow-up to meet their needs (Cancer Reform Strategy 2007, 2009). Current National Guidance (NICE 2009) recommends patients treated for breast cancer also have yearly mammograms if diagnosed up to 50 years of age and for those diagnosed after 50 for a minimum of 5 years. These recommendations follow observational studies which have shown that ipsilateral breast tumour recurrences (IBTR) are mainly detected by either by the patient themselves or by follow-up mammography. IBTR's detected by physical examination are uncommon and have a poorer survival than those detected by mammography (Taggart 2012). Attendance for surveillance mammography is associated with improved survival compared with women who do not attend for mammography follow-up. Detection of metachronous contralateral breast cancer by follow-up mammography has also shown to be associated with improved survival (Lu 2009). There is no clear evidence for the optimum frequency or duration of mammograms. In a screening setting, the frequency of mammography is determined by the lead time achievable. Mammography achieves longer lead times in older women compared to younger women because older women have more indolent tumours and less masking effect from dense breast tissue than younger women (Shen 2001). In addition, young age is a strong predictor for local recurrence after both invasive cancer and DCIS (Shaitelman 2012, van der Leij 2012, Hwang 2013). Type of breast surgery (mastectomy or conservation) does not affect long term survival but 3 years after diagnosis second breast cancers are found less frequently by mammograms in patients who had a mastectomy compared to those who had conservation surgery (Vooga 2001). For these reasons a study to assess if reducing the frequency of follow-up mammography is best carried out in women over the age 50. There have been no randomised controlled trials in this setting.

A recent HTA report (Robertson 2011) has confirmed from earlier studies that mammographic follow-up varies greatly across the UK and that some patients may require mammograms only three yearly provided they are monitored and supported in alternative ways. MRI is the most accurate method of imaging follow-up in women who have had breast cancer but the high cost and limited availability of breast MRI makes wide spread MRI follow-up impractical (Robertson 2011). Mammograms are limited to detecting new or recurrent breast cancers giving no information on physical, cosmetic or emotional wellbeing. A recent review showed that more than 25% of cancer patients have long term treatment related side effects like wound pain or arm swelling which may affect their ability to recognise and report recurrent disease (Murthy 2007, Hopwood 2010, Richards 2011). Whilst NICE 2002 Guidance recommended all asymptomatic patients be discharged by 3 years post-surgery, specialists were non-compliant as they "need to know" about these less favourable long term outcomes and value the feedback patients provide to help them improve future treatment for other patients (NICE 2002, Donnelly 2007, Jeevan 2011). Specialists may often assess their patients with regard to their "risk" or need for future support. That assessment will vary across the UK and will be assessed centrally to determine national consensus guidelines based on the results of randomisation. By 3 years post diagnosis most patients will have completed their curative and reconstructive treatment and should be well versed in self-assessment (Donnelly 2007, van Hezewijk 2011).

Factors suggesting a poor prognosis for women with ipsilateral breast tumour recurrences (IBTR) are not well established but include:

1. The presence of metastatic disease which may be occult but which is often diagnosed following imaging screening tests at the diagnosis of IBTR (e.g. CT of the chest, abdomen and pelvis)

2. An IBTR with poor histological features especially when compared to those of the primary tumour
3. A short period to IBTR (early IBTR has been reported to worsen outcome in comparison with late IBTR) (Lee 2011)
4. When an IBTR is thought to represent a recurrence rather than a new primary (Yi 2011)

It is important to characterise the histological factors of the IBTR and new contralateral breast tumours to fully understand the course of the disease.

The study will therefore assess if patients who have mammography every 2 or 3 years are no-worse off in terms of detection of recurrence or breast cancer specific survival as compared to patients who have annual mammograms. The study will take advantage of the introduction across the whole UK of Digital Mammography which is both quicker and more sensitive than conventional mammography.

Evidence explaining why this research is needed now

Survival from Breast Cancer has improved markedly in the last 20 years (Coleman 2008). This is to be celebrated and has been attributed mainly to earlier diagnosis and new treatments to prevent recurrence (Peto 2000). Incidence of Breast Cancer however continues to increase with 47,693 new cases among women in the UK alone in 2008 (Cancer Research UK 2010). The lifetime risk of breast cancer for women in the UK is now 1 in 8. This, combined with increased 10 year survival to over 73%, has resulted in an increase in the number of long term breast cancer survivors so that there are now over 550,000 women who have been treated for breast cancer living in the UK (Cancer Research UK 2010). Breast cancer remains a major public health problem and is the second most frequent cause of cancer death in women, with about 12,000 deaths in 2008 (Cancer Research UK 2010). 80% of women who develop breast cancer are older than 50 years at diagnosis and most deaths occur in this age group.

Survivorship after breast cancer and the medical, psychological and informational health needs of these patients have become increasingly recognised (Ganz 2002, 2004, 2008; Hopwood 2010). From the service provision perspective, improved disease free survival reduces the burden to health services for treatment for advanced cancer but increases the burden on specialist clinics for surveillance and for surveillance mammography. There is also an increased demand for reviewing patients who refer with potential symptoms of local recurrence or new cancers which are curable if diagnosed and treated early (Lu 2009, Richards 2011, NCIN 2012). Late recognition of recurrence is very expensive (Walkington 2012, Van Hezewijk 2012).

Follow up should encompass early detection of new cancers as well as recurrence and maximise adherence to preventive endocrine therapy in those patients with oestrogen or progesterone receptor positive cancers (Fontein 2012). Evidence that women with a history of breast cancer are at increased risk of a second breast cancer primary was confirmed in large populations with different health care systems (Ciatto 2008, IARC 132). Long term studies indicate that this increased risk continues at a constant rate for 20 years or more (Rojas 2005, Taggart 2012).

There is evidence that mammographically detected recurrences are also detected at an earlier stage and results in better survival than clinically detected ones and that local recurrence may occur many years after treatment (Taggart 2012). The finding that a regimen of surveillance mammography offers a survival benefit among women treated for primary breast cancer when compared with a surveillance regimen that does not include surveillance mammography was also reported in a recent Health Technology Assessment incorporating a systematic review. However due to the limited availability of data the studies reviewed and the lack of randomised controlled trials, no conclusions could be drawn about the optimum frequency or duration of mammography after surgery (Robertson 2011).

Whilst benefits and side effects of breast cancer treatment has been learnt from long term follow up of cohorts of patients in the specialist clinic, its contribution to improved outcomes remains unclear. Detection of local recurrence and contralateral cancers occurs more often by patients or by surveillance mammography than by routine clinical examination, and hospital based follow up does not meet patients' needs for psychosocial support. The increasing numbers of breast cancer survivors put pressure on services

that may be better directed to patients who are ill. Recent debate regarding the possibility of "over diagnosis" of breast cancer through screening has highlighted the pivotal role of long term tracking of cohorts of patients in evaluating the prognosis of small cancers (Zahl 2011, Gotzsche 2011). It may be possible in the future to identify tumour and patient characteristics which predict a very low risk (Cheang 2009, Perou 2000). This need not be a reason for hospital led follow-up. A patients ability to self-check and report concerns could be improved and cost less by using alternative follow-up regimens including questionnaires and contact with nurses, GPs, radiographers or internet access (Lu 2011, Lu 2012) Computerised tracking and linking of primary care records could enable this essential data to be recorded for research purposes (Ashley 2011).

In trials of alternative follow-up, after one year a significant proportion of patients were retained in hospital follow-up by oncologists (Grunfeld 1996, Grunfeld 2006). It is likely that patients requiring mastectomies and chemotherapy may not have completed treatment by one year after diagnosis, with over 20% reported to need re-excision (Jeevan 2012). Early discharge to alternative follow up at one year post diagnosis is likely to be suitable only for low risk patients who have had conservative surgery with no complications or need for reconstruction.

Addressing emotional and physical concerns are important parts of survivorship which should be incorporated into any follow-up plan regardless of location. Ganz recommends a self-held care plan (Ganz 2008). In the UK the universal population based primary care system – the National Health Service (NHS) - includes general practitioners, practice nurses, district nurses, health visitors and community psychiatric services which often work from the same health centres. Patient held care plans are successfully used for a variety of chronic conditions as a supplement to the NHS organisational structures and as an aid to communication. 'Fear of recurrence' has been identified as the most prevalent psychological and social unmet need in those living beyond cancer (Thewes 2011). This fear may become unceasing and overwhelming and inhibit people from investing financially or emotionally in the future or following their usual daily and social activities (Hansen and Tjørnhøj-Thomsen 2008, Herschbach, 2010, Balmer 2012). It may be of particular relevance to recruitment in Mammo-50 which will potentially involve less post-treatment surveillance. There are many scales to assess quality of life but there is not one which covers all domians (Kanatas 2012). Therefore, fear of recurrence will also be explored using the ACS short validated questionnaire (Gotay 2007) and unmet needs will be explored using the distress thermometer (Brennan 2011, NHS Improvement 2012) for a sub-set of patients. In addition empowerment of patients and patient reported outcome measures will be explored (Ashley 2011, Van den Berg 2012).

Generally women reported high satisfaction with alternative follow-up regimes (Vaile 2006, Beaver 2005, Chapman 2007). These studies did not report any consideration of age in the design or interpretation of the trials or details of how alternative follow-up was presented to the women and whether survival was discussed. It is likely that when survival and well-being are in conflict, such as in making decisions about stressful tests or preventive treatment which has side effects, patients may make different choices so that some inequalities will not depend on service availability (Clough-Gorr 2010). More research is needed into how well patients understand risk (Magee 2011) and how much they are prepared to allow their treating doctors to make medical decisions on their behalf, as well as the social differences and circumstances associated with these choices (Watson 2012).

A major issue in follow-up is the management of preventive hormone therapy and patient compliance (Fontein 2012). 75% of breast cancers are hormone dependent and thus susceptible to hormone therapy. In a survey of breast cancer specialists in the UK the management of this therapy was highlighted as the most important aim of follow-up (Donnelly 2007). Preventive treatment and the management of chronic disease is typically the premise of General Practice rather than the specialist unit at the hospital. In the light of new preventive treatments available, and the need to monitor long term side effects such as osteoporosis, it is likely that the majority of this care should be transferred to General Practice where informational needs for local support networks and other services could also be more easily met.

Breast reconstruction is an emerging theme in breast cancer follow-up with the Royal College of Surgeons national mastectomy and reconstruction audit showing significant variation in short-term outcomes

(Martin 2013) and patient satisfaction (Jeevan 2011). New implants also warrant long term follow-up (Martin 2013).

Compared with younger women, older women are more likely to have breast cancer with oestrogen receptor and progesterone receptor expression, with or without HER2 overexpression (Schonberg 2010). Variation in receptor status expression mainly exists between very young women (<35 years) compared with other age groups. There is less variation between age groups among postmenopausal women. ER positive cancers increase from greater than 60% among women aged 30–34 years to 85% among women 80–84 years (Anderson 2011). HER2-positive tumours decrease from 22% among women younger than 40 years to 10% in women 70 years or older (de Munck 2011). This confirms a more indolent biological behaviour of breast cancer amongst older women. Moreover, older age associates with the lowest local recurrence rate after mastectomy (Karlsson 2012). On the basis of these findings, it is not unconceivable that follow-up of breast cancer could be less aggressive in the older age sub-setting.

4. Trial Design

Multi-centre, randomised, controlled, phase III trial of annual mammography versus 2 yearly for conservation surgery patients and 3 yearly for mastectomy patients.
There will also be an observational cohort study offered to those patients for whom the specialist or patient opts for standard mammography per local practice or immediate discharge to the screening programme or stopping mammography altogether.
An integrated feasibility study will assess the willingness for centres and patients to participate in the trial and explore reasons for non-randomisation of the cohort patients.
All patients will be asked to complete the Mammo-50 participant questionnaire booklet and followed up in terms of recurrence and survival in accordance with the protocol.

5. Summary of Interventions

For the purposes of MAMMO-50, centres/units will utilise digital imaging in line with the National roll-out of digital screening mammography in 2010. Digital mammography offers advantages in terms of image quality, increased sensitivity in important subgroups (e.g. women with dense breasts) and reduced examination time that permits a greater opportunity for patient contact with the radiographer or breast care nurse. It is also reported to deliver significantly less radiation than conventional mammography.

In addition to the mammogram, eligible patients will be asked to complete the MAMMO-50 participant questionnaire booklet, delivered at the time of their mammogram or clinical follow-up, which will include questions on their general health, health resource use and adherence to prescribed maintenance therapy such as Tamoxifen or Arimidex. With the patients consent, the General Practitioners will be aware of their recruitment and any breast related consultations or referral to breast clinic during the period of the study will be screened using health records. Patients will remain in the NHS Breast Screening Programme throughout the duration of the trial but should not attend for their screening mammograms if invited. This is to prevent duplication and potential invalidation of the trial results.
All patients with breast cancer, both invasive and DCIS, should be given clear and concise information regarding their diagnosis and treatment and should be aware that if they get a new symptom they will be seen again urgently (within 2 weeks) in a specialist clinic (Cambridge model, Chapman 2007).

In addition the patient and public Involvement (PPI) component of the study will evaluate adequacy of current information offered as standard to patients as well as effective ways of collecting quality of life data for those patients consenting to be part of the QoL and/or qualitative sub-studies.

6. Aims and Objectives

Feasibility study aims:

- To set up at least 100 actively recruiting centres and/or a target recruitment of 1400 patients by month 24.
- To report user perspective and involvement.
- To develop and test the mechanisms for data capture through Health & Social Care Information Centre (HSCIC), Public Health England (PHE) and Hospital Episode Statistics (HES) whilst addressing possible contamination from the screening programme.
- Undertake a more detailed scoping exercise on the variation of current practice and develop cost-effectiveness models.
- To ascertain reasons for non-participation in the RCT.

Primary:

- To investigate the hypothesis that patients treated surgically with curative intent for invasive and non-invasive breast cancer, aged 50+ at diagnosis and more than 3 years post-surgery, will not be disadvantaged in terms of disease specific survival, recurrence, survival and quality of life by having surveillance mammograms 2 yearly after conservation surgery and 3 yearly after mastectomy, respectively.
- To assess cost effectiveness and develop a health economic model which measures real costs of reduced surveillance imaging and any additional follow-up consultations and investigations.

Secondary:

- To assess the timing and types of recurrence and characterisation of tumours.
- To identify and assess education, support and cost-effectiveness of alternative methods of follow-up (e.g. Radiographer-led or nurse-led).
- To use innovative ways of collecting outcome data away from traditional hospital based clinics through HES and Public Health England data linkage for breast screening.
- To determine compliance with national guidelines including hormone blocking treatment and bone health.
- To examine the acceptability to patients and clinicians of reduced surveillance imaging and follow-up package by focus groups and interviews.
- To develop models to predict recurrence and new primaries from presentation, pathological and radiological data.

7. Outcome measures

Primary outcomes:

- Disease specific survival
- Cost effectiveness

Secondary outcomes:

- Recurrence (time to recurrence, type of recurrence and features of recurrence plus new primary in ipsilateral breast and new primary in contralateral breast) using questionnaire and data linkage. The NCIN lead registry for breast cancer will match the MAMMO-50 cohort against the national cancer registration database at 3-yearly intervals for 3 years (3, 6 and 9 years after randomisation). Details of recurrent breast cancers (local, regional and distant) will be provided as will dates and causes of death where appropriate. The histological characteristics of ipsilateral

breast tumour recurrences (IBTR) and contralateral new primaries will be recorded and the Nottingham Prognostic Index (NPI) calculated and compared to the NPI of the original tumour. These characteristics will include invasive and in situ tumour size, histological grade, histological type, vascular invasion status, ER, PR and HER-2 status, in those tumour treated by immediate surgical resection. Nodal status will be recorded in those who have a further nodal procedure. In tumours treated with systemic therapy and no surgery (this is common if metastatic disease is found at the time of recurrence) tumour type and grade and receptor status will be ascertained from the diagnostic core biopsy and lesion size estimated from imaging

- Number of referrals back to the hospital system
- Long term survival (20 years post-surgery) using ONS flagging

Outcomes for sub-studies:

- Quality of Life and Patient concerns using the distress thermometer and ACS fear of recurrence scale
- Patient experience of support provided for rapid assessment of new symptoms
- Experience of follow-up strategies assessed by patient, specialist, breast nurse & GP
- Compliance with guidelines (e.g. bone health, adjuvant hormone blocking therapy)
- Pathology biomarkers and tumour characteristics

8. Patient Selection & Eligibility

Female patients previously treated surgically with curative intent for excised invasive or non-invasive (DCIS) breast cancer in breast cancer centres/units in the UK. Patients will be 50 years or over at initial diagnosis and 3 years post-surgery, having previously had surveillance mammograms per local practice.

a) Inclusion Criteria

- Female, age ≥ 50 years at initial diagnosis
- Excised invasive or non-invasive (DCIS) breast cancer with local treatment completed
- 3 years post curative surgery (trial entry date must be between 36 to 44 months of the first therapeutic operation)
- No evidence of local recurrence or new breast cancer primary (confirmed by 3rd year mammogram), distant metastases or any new malignancies
- Written informed consent for the study

b) Exclusion Criteria

- Evidence of local recurrence or new breast cancer primary (confirmed by 3rd year mammogram at year 3), distant metastases or any new malignancies since index tumour
- Previous diagnosis of a breast malignancy prior to the index tumour
- Previous diagnosis of any non-breast malignancy unless:
    - managed by surgical treatment only and disease free for 10 years or
    - previous basal cell carcinoma of skin or
    - previous cervical intraepithelial neoplasia
- Bilateral breast cancer including DCIS
- Known BRCA or genetic mutation
- Classical LCIS

c) Informed Consent

It is the responsibility of the local Principal Investigator (or designee as listed on the Site Responsibilities Form) to obtain written informed consent in compliance with national requirements from each patient prior to entry into the trial. The trial must be discussed in detail with the patient, and the patient provided with a copy of the Patient Information Sheet. Patients should be offered sufficient time to consider the trial, allowing time for discussion with family/friends/GP. The patient must be given the opportunity to ask questions and to be satisfied with the responses prior to written consent being given. Either postal consent or face to face consent is acceptable.

A copy of the signed Consent Form(s) must be given to the patient. The documents are available in electronic format to facilitate printing onto local headed paper. Original Consent Forms must be retained on site (it is recommended that the original is retained in the trial site file, with a copy filed in the relevant patient's hospital notes). Completed Consent Forms must not be sent to the Trial Office at WCTU.

If the Patient Information Sheet and/or Consent Form are modified during the course of the trial, sites will be notified of the procedure to follow for patients already consented and for prospective patients.

For patients who decline entry into the main randomised trial, they will be offered the opportunity to enter the observation cohort study. This will require written informed consent to be obtained according to the principles above.

9. Randomisation Procedure

The randomisation procedure will commence at the time consent has been given ('trial entry'). Before contacting the MAMMO-50 Trial Office at Warwick Clinical Trials Unit (WCTU), a Randomisation Form and Eligibility Form must be completed.

For patients who agree to participate in the observational cohort study, the site will be required to complete a Registration Form which will request the same information as the main trial. These data will be entered into the MAMMO-50 database.

To preserve the patient's anonymity, only their allocated trial number and initials will be required on the CRFs. With the patient's permission, their initials, date of birth, and health service (NHS) number/Community Health Index (CHI) number will be collected by the Trial management team at registration on the randomisation/registration form to allow flagging with Health & Social Care Information Centre and the Office of National Statistics. Patients should be assured that their confidentiality will be respected at all times.

These details can be phoned or faxed to the Trial Office:

Warwick Clinical Trials Unit
Telephone 024 7615 0402 (Mon-Fri, 9am-5pm)
Fax: 024 7615 1586

Patients will be stratified according type of surgery, DCIS or invasive disease, age and hormone therapy at randomisation. This information must be available at randomisation/registration.

Once eligibility has been confirmed through the randomisation system, the patient will be allocated a unique trial/registration number. The Trial Office will then send a confirmation fax containing the randomisation/registration details. The randomisation system will ensure that there is no bias between the two trial groups. Patients will be randomised strictly sequentially, and treatment allocation between arms will be undertaken at a ratio of 1:1.

a) Randomisation/Registration Documentation

After patients have been registered/randomised, the investigator should send the patient's General Practitioner (GP) a letter and copy of the Patient Information Sheet to inform them of their participation in the trial.

The Randomisation/Registration Form and Eligibility Form must be sent to the MAMMO-50 Trial Office. The patient's details (initials, date of birth and NHS number or CHI number) must be entered onto the local site's Patient ID Log. The patient's trial/registration number and initials will be used on all subsequent CRFs and correspondence relating to that patient.
A Screening Log must be maintained to document all patients considered for the trial including those subsequently excluded. Where possible, the reason for non-entry to the trial must be documented. This must be faxed to the Mammo-50 Trial Office on a regular basis as requested. Patient names or hospital numbers must not be recorded on the Screening Log (use initials only).

10. Pathology

All patients in the Mammo-50 study will be asked to 'gift' a sample of their tissue from the original surgery, new primaries and any future recurrence for further research associated with the Mammo-50 study. Patients will be asked to consent for future (unspecified) research to be performed on their tissue samples, which will be pseudo-anonymised. This research may include exploration of biomarkers or identification of intrinsic breast cancer subtypes (e.g. luminal, basal, HER2). In the case of subsequent relapse or new primaries, prospective consent will be obtained for a sample if possible. Consent to the pathology sub-study is optional. In the event of such permission being given, tumour samples will be retained in the local pathology departments until the licensed MAMMO-50 Tissue Bank is established.

11. Data Collection

The Case Report Form (CRF) will comprise a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details. Data collected on each patient must be recorded by the local Principal Investigator, or his/her designee, as accurately and completely as possible. The Principal Investigator is responsible for the timing, completeness, legibility, accuracy of the CRF. The Principal Investigator must allow study staff access to any required background data from hospital records (source data e.g. medical records) on request. All data submitted on CRFs must be verifiable in the source documentation. Any deviation from this must be explained appropriately. CRFs are expected to be completed within 4 weeks of their due date.

This trial will use an electronic data capture (EDC) system which will be used for completion of the CRF. Access to the EDC system will be granted to approved site personnel via the Trial Office. If the use of a paper CRF is required, completed forms should be sent to the Trial Office and copies retained on site.

a) Mammo-50 Participant Questionnaire Booklet

The first Mammo-50 participant questionnaire booklet, which will include general questions, Health Resource Use forms and EQ-5D-5L, must be given to patients after written consent is obtained *but prior to randomisation*. Further Mammo-50 participant questionnaire booklets will be administered annually from date of 3rd year mammogram for more frequent mammogram schedule and 2 or 3 years for the less frequent mammogram schedule, up to 9 years post curative surgery.
Each participating site will be responsible for providing patients with the MAMMO-50 Participant Questionnaire booklets. The local researcher or their delegated staff member must explain the requirements, ensure the patient understands how to complete the questionnaires and the time-frames within which they are required, and (if the patient has completed them at home) ensure the booklets are returned to the MAMMO-50 Trial Office at WCTU following completion (via the local site if required). The member of staff responsible for this must be appropriately recorded on the Site Responsibilities Form and are responsible for sending reminders to patients to ensure maximum return of booklets.

b) Mammo-50 Participant Quality of life Booklet

Patients agreeing to participate in the Quality of life sub-study will be asked to complete a participant quality of life booklet at baseline (before randomisation/at registration) and then annually from the date of trial entry (defined as the date of randomisation or registration) for 7 years . The Quality of life booklet includes the distress thermometer, Assessment of survivor concerns fear of recurrence scale, Warwick-Edinburgh Mental Well-being Scale (WEMWBS) and the Functional Assessment of Cancer Therapy for breast cancer (FACT-B+4).

As a duty of care high levels of distress will be reported to the principal investigator at each site for the consideration of the clinical team who may wish to either contact the patient directly, contact the GP or discuss at the next patient follow-up appointment

c) Schedule of Delivery of Intervention

Mammographic surveillance will be for 9 years from date of curative surgery (or 6 years from date of trial entry) as per randomisation schedule. All patients must have a baseline 3 year post curative surgery mammogram prior to randomisation/registration. Sites must complete the study CRFs alongside the participant questionnaire booklets. The Mammo-50 participant questionnaire booklet must be completed at baseline (before randomisation/at registration) and as per scheduled mammogram thereafter, as stated above.

Telephone follow-up is permitted for patients who have been discharged from clinical review. It is planned that information will also be obtained where possible from Hospital Episode Statistics (HES) in conjunction with the National Cancer Intelligence Network (NCIN). Patients will also be flagged with the Health & Social Care Information centre and Office for National Statistics (ONS) for long term follow up. In the event of recurrence, second primary or death, the corresponding CRF must be completed.

Table 3: Schedule of Assessments

Applicable to:	Assessment	Pre-Rand	Post-Rand	1 year from 3rd year mammogram date (Year 4)	2 years from 3rd year mammogram date (Year 5)	3 years from 3rd year mammogram date (Year 6)	4 years from 3rd year mammogram date (Year 7)	5 years from 3rd year mammogram date (Year 8)	6 years from 3rd year mammogram date (Year 9)	
All participants	**Local inclusion criteria satisfied**	X								
	Informed consent taken	X								
	Participant questionnaire booklet [a]	X								
	On-study, treatment history and pathology forms completed		X							
	Annual follow-up form [b]			X	X	X	X	X	X	
Standard arm (annually)	**Surveillance mammogram** [b, c]			X	X	X	X	X	X	
	Participant questionnaire booklet [a]			X	X	X	X	X	X	
Conservation surgical group (2-yearly)	**Surveillance mammogram** [b]				X		X		X	
	Participant questionnaire booklet [a]				X		X		X	
Mastectomy surgical group (3-yearly)	**Surveillance mammogram** [b]					X			X	
	Participant questionnaire booklet [a]					X			X	
		Pre-Rand	**Post-Rand**	**1 year from trial entry** [d] (Year 4)	**2 years from trial entry** (Year 5)	**3 years from trial entry** (Year 6)	**4 years from trial entry** (Year 7)	**5 years from trial entry** (Year 8)	**6 years from trial entry** (Year 9)	**7 years from trial entry** (Year 10)
Quality of Life sub-study participants	**Quality of Life booklet** [e]	X		X	X	X	X	X	X	X

a. Participant questionnaire booklets are completed annually from the date of the third-year mammogram. Questionnaires can be completed at clinic follow-up visits, via telephone follow-up or posted to the participant for completion.

b. During the coronavirus pandemic some mammograms were delayed. For participants in the standard arm, receiving annual mammograms, the schedule for future mammograms will be adjusted to align annually with this delayed date. Therefore, affected participants' future mammograms will no longer align to the date of the third-year mammogram. The digital mammography form and annual follow-up form should be completed at the time of the surveillance mammogram.

c. Results of surveillance mammograms are recorded on a digital mammography form.

d. Trial entry is defined as the date of randomisation/registration

e. Quality of life booklets are completed by the participant. The booklet includes distress thermometer and fear of recurrence scales.

12. Post Randomisation Withdrawals, Exclusions and Moves Out of Region

Patients have the right to withdraw from the trial at any time for any reason. Patients should be encouraged to remain within the trial, however, if a patient wishes to withdraw from the trial, the MAMMO-50 Trial Office should be notified immediately. Full details of the reasons for withdrawal must be recorded on the relevant CRF(s). Patients may be withdrawn from the interventions at the discretion of the Investigator and/or Trials Steering Committee due to safety concerns. If a patient is only withdrawn from the intervention, they must be followed-up in accordance with the protocol. Patients moving away from the region of the local site should NOT be withdrawn from the trial. Should this occur, please contact the MAMMO-50 Trial Office with details of the relevant patient, and they will endeavour to assign the patient's follow-up to a site close to their new location.

13. Statistical Considerations

a) Stratification

Randomisation will be stratified by

- type of surgery (conservation, mastectomy),
- DCIS or invasive disease,
- age at randomisation (53-<55, 55-75, >75 yrs),
- hormone therapy at randomisation (continued, stopped, never started (including ER-ve or DCIS).

In addition mandatory information on known risk factors for recurrence/new primaries such as margin involvement, lymph node status, vascular invasion, histological grade, invasive tumour size, ER status as well as treatment history, and breast density will be collected.

b) Power and Sample Size

Sample size: Assuming that patients who have survived and are recurrence free at 3 years post-surgery have a 5 year disease specific survival for the next 5 years of 89%, then recruiting 5000 patients (2500 per arm) will allow detection of non-inferiority with a 2.5% 1-sided significance and 90% power, defining non-inferiority as no worse than 3% below the standard arm.

This sample size would also allow the detection of non-inferiority in the time to recurrence with 2.5% 1-sided significance and a 90% power. These calculations assume that patients who have survived and are recurrence free at 3 years post-surgery have a rate of recurrence after 5 years on study of 8% or less, non-inferiority is defined as no worse than 2% below the standard arm. This would also allow differences of 2% to be detected in the time to recurrence rates at 5 years with 90% power at the 5% significance level.

A Quality of Life sub-study of at least 600 patients would be sufficient to detect a relatively small standardised difference of 0.3 with 90% power and 5% 2-sided significance level. For example, this would equate to a 7.5% change in quality of life assuming a conservative standard deviation of 25%.

c) Statistical analysis:

The primary outcome of disease-specific survival is defined as the time from the date of trial entry until the date death from disease, or censored at the date of death from other causes or date last known to be alive. Kaplan-Meier survival curves will be constructed for each trial arm and Cox proportional hazards models will be used to compare trial arms after adjustment for stratification variables as well as exploring important prognostic factors. All analyses will be carried out on an intention-to-treat basis.
Patterns of relapse will be explored. The time to recurrence is defined as the time from the date of trial entry until date of first loco-regional recurrence or new primary in ipsi- or contra-lateral breast or censor date. The time to distant recurrence will also be calculated separately. Overall survival will be calculated from the date of trial entry to the date of death, or the censor date. The time to event secondary outcomes

will be assessed using Kaplan-Meier survival curves and Cox proportional hazards models to compare trial arms and explore important prognostic factors. Frequencies of the number and types of recurrence (including new primary in ipsi- or contra-lateral breast) and features of recurrence will be recorded and compared where appropriately using the Chi-squared test.

The characteristics of ipsilateral tumour recurrences and contralateral new primaries will be compared across trial arms using a chi-squared test and changes from the baseline tumour characteristics reported.

Possible over diagnosis by mammography will be estimated by recording the proportion and frequency of ipsilateral breast tumour recurrences and contralateral new primaries which are either low grade DCIS or grade 1 invasive tubular cancers as these lesions constitute those lesions most likely to show an indolent or non-progressive behaviour pattern. These frequencies will be compared across trial arms using a chi-squared test.

Number and reasons for referrals back to the GP or hospital system will be reported.

Psychological assessments and Quality of Life will be scored using the appropriate manuals and assessed using longitudinal methods and appropriate statistical tests depending on the level of missing data.

Screening logs of eligible patients will be assembled using simple flow charts and counts to display numbers and percentages of patients at each stage of the eligibility and recruitment processes.

14. Trial timetable and milestones for MAMMO-50

MAMMO-50 will randomise 5000 patients from NCRN research networks in the UK. Up to 2000 additional patients will be registered in the cohort study. An integrated feasibility study will assess the willingness for centres and patients to participate and will require at least 100 centres/units and/or 1400 patients randomised within the first 24 months. All centres will be asked to provide screening logs which should include number of patients screened, reasons for refusal and any issues at randomisation. Recruitment rates will be regularly checked to see if any additional training or interventions are required to improve rates at poorly recruiting sites, and to share best practice from the top recruiting sites.

Months 0-6: Grant activation and trial set up. Purchasing computers and equipment.
Preparation of trial documentation, including site initiation documents and case report forms. Site initiations for 30 cancer centres. DMEC/TSC meeting prior to starting recruitment.
Month 7: Launch meeting. First patient randomised.
Month 18: 100 cancer centres open; 750 patients, IDMEC meeting to monitor recruitment and contamination from screening. TSC meeting for trial oversight, progress and recruitment.
Month 24: 1400 patients recruited. DMEC meeting to assess trial feasibility phase.
TSC meeting for trial progress, recruitment and assess feasibility phase. Feedback to funder via DMEC and TSC chairs. Feedback from funder with default of continuing unless requested to stop.
Month 27: Revised recruitment figures approved. DMEC/TSC email review
Month 32: Recruitment of 1653 HTA review.
Month 42: Recruitment of 2388 patients. DMEC/TSC meetings
Month 54: Recruitment of 3478 patients DMEC/TSC meetings
Month 60: Recruitment of 4058 patients.
Month 68: Recruitment of 5000 patients.
Months 68 -123: Follow-up of patients and data collection & data cleaning.
Months 101: Data cleaning and analyses of interim analysis of 3 year disease specific survival
Months 124 - 126: Final analysis with 5-years median follow-up on all patients, preparation of HTA report and manuscript, presentation at Clinical National and International conferences, dissemination through patient and consumer groups.

15. Economic Evaluation

All patients will be contacted at the time of their scheduled mammogram to complete the Mammo-50 patient questionnaire booklet which includes the EQ-5D-5L and brief questionnaire regarding their general health. For those patients who are discharged from clinical follow-up, postal questionnaires and telephone follow-up is acceptable. The economic analysis will focus on (1) within trial cost effectiveness analyses, and (2) a lifetime decision analytical cost effectiveness model. Both will be undertaken from the perspective of health and social care sector.

Within trial cost effectiveness analyses: Incremental cost effectiveness ratios will be presented using (i) disease free survival and (ii) QALYs. The estimation of QALYs requires the production of utility weights for each health state observed in the trial population. EQ-5D-5L is an updated version of the EQ-5D measures health status in 5 dimensions plus a visual analogue scale of self-rated health state. This instrument is reported as valid and reliable for the estimation of health utility in people with cancer (Pickard 2007).

The EQ-5D-5L is a very simple instrument to complete and will therefore be collected at baseline and at the time of scheduled mammogram visits until the end of follow up. Where events have occurred, the EQ-5D-5L will be collected by the research nurse as part of the events form. This will limit the need to interpolate quality of life between observation points and the associated inaccuracy in the estimation of the health related quality of life differences between the arms (Manca 2006).

Measurement of resource use: NHS resource use associated with each modality will be collected through Hospital Episode Statistics. Unit costs for health service resources will be obtained from national sources such as the NHS Reference cost database. Where national unit costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimate in the analysis. The cost effectiveness analysis will adopt the perspective of the NHS and social services.

The analysis will adopt the recommended approach to discounting costs and benefits. Under current recommendations this would mean that costs and outcomes would be discounted at 3.5% per annum (Brouwer 2005, Claxton 2006). In respect of uncertainty the non-parametric bootstrap method will be used to produce a within-trial probabilistic sensitivity analysis of the incremental cost effectiveness ratio. In addition to presenting the expected incremental cost effectiveness ratio, we will present the scatterplot on the cost effectiveness plane, the 95% cost effectiveness ellipse and the cost effectiveness acceptability curve (Drummond 2005).

A long term cost effectiveness analysis is required to capture the full impact of any difference in mortality between the arms. The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the study team but it is likely that the model will be a Markov or semi-Markov state model. As far as possible the transition rates for the model will be estimated from the clinical trial data. For model parameters for which data could not be collected within the trial; e.g. long term outcomes, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature (NICE methods Guide 2008, Weinstein 2003) including data from the National Cancer Intelligence Unit (NCIN). The long term cost effectiveness modelling will adopt the strategies for addressing issues of perspective and discounting as the within trial analysis. HES (Hospital Episode Statistics) data will provide details hospital admissions, outpatient visits, critical care and treatment to contribute to the health economics analysis of additional health costs related to the frequency of surveillance, treatment and the study.

16. Patient and Public Involvement

A breast cancer follow-up workshop for patients and professionals was held at Warwick in 2008 to discuss and obtain patients' and professionals' opinions of current follow-up strategies after breast cancer.

Maggie Wilcox (Mammo-50 patient representative) and the NCRI breast cancer clinical study group user representatives have been influential in defining the acceptability of the current trial design, together with the charity ICPV (http://www.independentcancerpatientsvoice.org.uk/). It is indicated that patients want choice of follow-up and continuity of care and are willing to be discharged from hospital based clinical examination if they have a quick route back to their specialist breast care nurse. The previous ibreast HTA proposal concentrated on follow-up strategies which were underpinned by annual surveillance mammography. It is clear that the current feeling is to allow patients with a very low risk of recurrence to be discharged back into the screening programme (i.e. 3-yearly surveillance mammography). High risk younger patients are kept in the system longer. It is the moderate risk patients for whom there remains uncertainty as to the optimal duration and frequency of surveillance mammography.

Maggie Wilcox has been involved in the discussions regarding the design of the study and as Co-investigator assisted with the preparation of the application. Patient involvement is fundamental to this study as is patient acceptability and experience of proposed follow-up strategies. Involvement of the patient and public ensures that the design is acceptable, the questions the trial addresses are important to patients and the patient information sheet is clear and understandable for patients. Patient representatives will be invited to take part in focus groups to assess the acceptability of follow-up and mammographic surveillance and to help develop creative ways to communicate information to patients and the public. Within the 24 months feasibility study the patient group will assess the quality of life scales proposed in the QoL sub-study. In addition a follow-up on-line survey will be developed and circulated by ICPV aimed at gathering information about follow-up experience (i.e. patients gathering information directly from patients). Once completed, the survey will be stored electronically on the servers at Warwick CTU. Patients should be assured that their confidentiality will be respected at all times.

Focus groups are planned with the patient advocacy group to discuss the results of the study and plan how best to disseminate the findings to consumers. Patient representatives, including Lesley Turner, will also ensure that the results of the study are disseminated through their contacts, other patient representatives and websites including www.independentcancerpatientsvoice.org.uk. In addition, dissemination will also be carried out through the NCRN Consumer Liaison Group and INVOLVE conferences.

17. Qualitative sub-study (QSS)

The aim of the qualitative component of Mammo-50 is to assess the acceptability and experience of mammographic surveillance to women 50 years and over at initial diagnosis with breast cancer and to devise relevant and appropriate ways to communicate information to this group.

Study 1: Interviews with women

Aim:

The aim is to carry out an in-depth exploration of women's (women 50 years or older at initial diagnosis who have had potentially curative surgery for breast cancer) experiences and views of different models of follow-up and mammographic surveillance.

Objectives:

To explore:

1. Women's views on mammographic surveillance and the importance of mammography to them
2. Women's views on follow-up and the importance of follow-up to them
3. Issues of concern / importance to women previously treated surgically for breast cancer (physical, psychological, emotional, social)
4. Information provision at end of treatment; understanding of risk of recurrence; confidence regarding ability to self-manage / when to seek help
5. Experience of support provided for rapid assessment of new symptoms

Design

Longitudinal, qualitative study

Method

In-depth, semi-structured interviews will be conducted and audio-recorded with participants, eligible for recruitment to Mammo-50, including those who accept or reject randomisation. Interview topic guides will be used to ensure similar areas are covered in each interview within each group, based on those used in previous studies but also encouraging the informants to express their own views about Mammo-50.

Sample and Frequency

Participants in Mammo-50 will be asked to indicate on their consent form if they would be willing to take part in an interview study. We will seek to interview around 10-15 women from each of the three study groups (annual, 2 yearly, 3 yearly mammograms). Purposive sampling will be utilised, striving for a mix according to geographical location, age, employment status, ethnicity, and size of screening centre, baseline questionnaire responses. Women will be interviewed again towards the end of the trial. We will also seek to interview a sample of women who declined to participate in Mammo-50, or who choose to discontinue in the reduced surveillance arms of the study, striving to recruit from different geographical locations in the UK; from large vs small screening centres (which may use mobile units); patients ≥50 – 65 and > 65 years; employed vs unemployed.

Analysis

Interviews will be recorded, transcribed and analysed using a Framework Approach. A thematic framework will be developed using a priori issues and questions from the aims of the study and new themes raised by participants within the interviews. The framework will be applied to the text of the interviews and the coded data from each interview will be arranged on a chart according to each issue/theme identified. Associations and differences between themes will be examined with a view to providing explanations of the participants' experiences and understandings. Comparisons will be made between groups of women and over time.

Computer software will be used to organise the data for analysis (e.g. NVivo). Analysis will be a collaborative process between the interviewer and the qualitative advisors.

Study 2: Interviews with Health Professionals

Aim:

To explore the views and experiences of health professionals regarding breast mammographic surveillance as part of breast cancer follow-up, with a focus on and participation in Mammo-50.

Participants:

Breast surgeons, oncologists, breast care nurses, radiographers, GPs

Method

Survey +/- interviews

Sampling

Subset of sites striving to recruit from different geographical locations in the UK; from large vs small screening centres (which may use mobile units).

18. Data Management & Patient Confidentiality

a) Data Acquisition

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. The Case Report Forms (CRFs) will be designed by the trial manager in conjunction with the Chief Investigator and Statistician. Original CRFs must be sent to the coordinating team at WCTU and copies retained on site.

b) Data Quality Monitoring and Audit

On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried with the site for resolution. Data will be entered onto the trial database and any further anomalies will be identified and queried with the site. Periodically, data will undergo additional checks to ensure consistency between data submitted on CRFs.

Trial staff will maintain regular communication with sites, through routine calls, mailings and/or meetings. In the event of persistent issues with the quality and/or quantity of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. The representative from the MAMMO-50 Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and to determine the site's future participation in the trial.

An audit may be arranged at a site if the Trial Management Group feels it is appropriate. Audits will be conducted by an independent team, determined by the Trial Management Group.

c) Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their allocated trial number and initials will be recorded on the CRFs. Date of birth will be used as an initial identifier for pathology samples and pathology forms. With the patient's permission, their initials, name, date of birth, address and health service (NHS) number/Community Health Index (CHI) number will be collected by the MAMMO-50 Trial Office to allow data linkage with Health & Social Care Information Centre and flagging with the Office of National Statistics and Public Health England, sample tracking and postage of questionnaires for those who do not complete them in clinic. In addition, with the patient's permission, they may be contacted to be interviewed about their decision to enter the trial (or not). Interviews will be audio recorded and will be stored electronically and identified by trial number only. Patients should be assured that their confidentiality will be respected at all times.

The local investigator must maintain documents not for submission to the trials unit (e.g. patients' written consent forms) in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected. Warwick Medical School Clinical Trials Unit will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment.

The database will be set up by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer, statistician and trial manager.

d) Data shared with third parties

Anonymised mammograms and tissue samples from the participant's original surgery and any future recurrences will be collected and the information will be shared with research collaborators, if necessary as part of this trial.

e) Data Storage and Archiving

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

Trial documentation and data will be archived for at least five years after completion of the trial in accordance with WCTU SOPs.

19. Trial Organisation

a) Trial Management Group (TMG)

The TMG includes a multidisciplinary team of clinicians, statisticians, a translational scientist and a patient advocate who have considerable expertise in all aspects of design, running, quality assurance and analysis of the trial. This group includes co-investigators as well as experts co-opted for their expertise. It is anticipated that the TMG will meet monthly by teleconference during the recruitment phase and as required during follow-up, dissemination and publication.

b) Trial Steering Committee (TSC)

The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year determined by the trial milestones (see section 14). Routine business is conducted by email, post or teleconferencing. Members of the TMG will be co-opted onto the TSC as appropriate.

The Trial Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the IDMEC
- Informing and advising on all aspects of the trial

c) Independent Data Monitoring and Ethics Committee (IDMEC)

An independent data monitoring and ethics committee will be established for this trial. The IDMEC will review trial progress, recruitment, protocol compliance and interim analysis of outcomes (not formally tested outside of the trial statistical analysis plan to be agreed with the IDMEC), annually or more frequent if requested, in line with the trial milestones (see section 14). The IDMEC will advise on whether the trial should continue, be amended or stopped prematurely based on the trial data monitored and any future publications or emerging worldwide evidence.

d) NCRI Clinical Studies Group

NCRI Breast CSG members developed and approved the trial, and provided input into responses to reviewers of the outline application.

e) Administration

The Chief Investigator for the trial is Janet Dunn, University of Warwick. The trial will be co-ordinated from the Mammo-50 Trial Office at Warwick Clinical Trials Unit (WCTU), under the direction of Professor Janet Dunn. Professor Andy Evans (radiologist) and Mr Peter Donnelly (Surgeon) will provide the radiological and surgical expertise, respectively. Clinical responsibility will be undertaken by the Lead Investigators of the Trial Management Group.

f) Site Staff Training

Prior to activating a site to recruitment, it is necessary for all staff members working on the trial to participate in an induction session. This will be carried out during the initial launch meeting. For sites unable to attend the trial launch, or for sites opening to recruitment at a later date, this will be carried out via telephone conference or by a site initiation visit.

An accreditation checklist will be completed for all sites to confirm that pre-activation activities have been completed and all relevant staff members are able to participate.

Support will be offered to staff at participating sites to ensure they remain fully aware of trial procedures and requirements. Additional support and training will be offered to sites where necessary (e.g. recruitment rate lower than expected).

20. Patient Protection & Ethical Conduct

The trial will be conducted in accordance with the principles and guidelines of the Medical Research Council (MRC), Good Clinical Practice (GCP), UK legislation, Warwick Clinical Trials Unit SOPs and the Protocol. GCP-trained personnel will conduct the trial. Free GCP training will be given, through the local National Cancer Research Networks (NCRN), to sites who do not have experience in conducting randomised, prospective, controlled, clinical trials.
Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by Warwick Clinical Trials Unit.
Patients' participation in the trial must be documented in the patient notes and must be communicated to the patient's GP.

a) Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial in the UK. UK NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. All sites should ensure that they carry insurance allowing them to conduct studies including this one.

The University of Warwick will indemnify the trial in relation to the design and management of the research.

b) Ethical & Regulatory Review

Mammo-50 has obtained ethics approval from Coventry & Warwickshire Research Ethics Committee (main REC) in the UK. The local Principal Investigator must submit this protocol, any supporting documentation and any amendments, to the R&D Office at the Trust (e.g. R&D), as appropriate in accordance with local requirements and recommendations made by the main REC.

c) Annual Report

Mammo-50 Trial staff will send an annual trial update report to the main REC. It is the responsibility of each site to send a copy of this report to the R&D Office in accordance with local requirements and recommendations made by the main REC. Any additional local information required must also be submitted. Additional data required by NHS Trusts are available from the Mammo-50 Trial Office on request.

d) Protocol Amendments

All agreed substantial protocol amendments will be documented by the Mammo-50 Trial Office and will be submitted to the main REC for approval prior to submission to local parties as appropriate. Each trial site must ensure that they are using the most up to date version of the protocol, the Patient Information Sheet and Consent Form. All previous versions of the protocol, and other trial documents should be crossed out with 'this version is now superseded' written on cover page.

21. Research Governance

a) Sponsor

University Hospitals Coventry and Warwickshire and University of Warwick will act as Co-Sponsors for the MAMMO-50 study.

b) Essential Documentation

A Trial Master File will be set up and held securely at the WCTU, in accordance with WCTU SOPs.

c) End of Trial

The end of trial is defined as the date of completion of all trial procedures on all participants.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the IDMEC
- Funding for the trial ceases

The Main Research Ethics Committee will be notified in writing within 15 days if the trial has been concluded or terminated early.

d) Financial Support

MAMMO-50 has been funded by a grant from HTA.

22. Dissemination & Publication

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team at the WCTU, and the final version will be agreed by the HTA before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

The trial will show whether or not continued annual surveillance mammography is needed 3 years post curative surgery, by which time most women have been discharged from hospital follow-up. There are very little data to support continued annual surveillance mammography and this trial aims to fill the evidence gap. In addition there is huge disparity in follow-up protocols adopted nationally and this project will provide information as to the type of follow-up adopted at each centre and acceptability to patients.

The results will be presented at national and international meetings and widely disseminated amongst the research community. This will generate publications in high impact journals.

The patient involvement is fundamental to this study. Our patient representative will ensure that the results of the study are disseminated through her national contacts, other patient representatives and websites including www.independentcancerpatientsvoice.org.uk. Our experience with working with the patient group is that many recruitment barriers are identified and solutions found within the early part of the trial. The focus groups, workshops and study days addressing barriers to recruitment, pathways and information flow will be presented at INVOLVE or MRC methodology conference or Society for Clinical Trials.

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