The MARECA study

National study of **ma**nagement of breast cancer locoregional **re**currence and oncologi**ca**l outcome

MARECA

Locoregional Recurrence Study

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Study overview

Although the 5 year breast cancer survival rate in the UK is considered favourable at 86.6%, patients continue to develop breast cancer recurrence within the same breast after breast conserving surgery, as well as in the remaining skin or chest wall after mastectomy. Patients also present with breast cancer recurrence in the nearby lymph glands (axilla, supra- or infra-clavicular, or internal mammary chains). These recurrences are collectively termed locoregional recurrence (LRR). It is estimated that up to 8% of breast cancer patients are diagnosed with LRR within 10 years of their original diagnosis.

Currently there is a lack of high-quality data and clinical guidance for the optimal management of breast cancer patients diagnosed with LRR. Additionally, there is a need to identify prognostic factors which will enable tailored treatment in order to improve patient outcomes. This was identified as a research priority at the 2019 Association of Breast Surgery Gap Analysis meeting. In the UK, breast cancer recurrence is under-reported to national cancer registries at individual hospital level (2020 annual report National Audit of Breast Cancer in Older Patients). As a result, retrospective analysis of existing routine data sources is unlikely to provide data on patient management that is representative of current national practice.

The MARECA study is a prospective, observational, multicentre, longitudinal cohort study which will determine LRR frequency and the current management and prognosis of patients diagnosed with breast cancer LRR +/- distant metastasis in the UK, with the aim of establishing best practice and informing future national guidelines. Over 50 UK breast units will participate in the study and recruit patients for 24 months with an aim of recruiting at least 500 patients. Data will be collected detailing the tumour pathology, imaging results, surgical treatment, radiotherapy, and systemic therapy of the primary and recurrent breast cancer.

Establishing a prospective cohort of patients newly diagnosed with LRR +/- distant metastasis will enable description of current multidisciplinary patient management, identify any potential geographical variations in patient care, and investigate risk factors associated with LRR development (including those related to the primary breast cancer and its management). The study participants will be followed up at two time points (3 and 5 years) in order to determine oncological outcome and evaluate potential prognostics factors, including stratification of LRR as a true recurrence or a new primary breast cancer. Specifically, we will investigate whether the type of surgery performed for the primary breast cancer (breast conserving surgery and radiotherapy vs. mastectomy) influences subsequent prognosis in patients diagnosed with locoregional recurrence.

The study results will aim to address the current knowledge gap and identify subgroup of patients who have less successful treatment outcome. This will direct future research and inform the design of future interventional trials and translational studies.

Table of Contents

Study overview 3
1. Background 6
1.1 The current national status 6
1.2 Known risk factors for locoregional recurrence 8
1.2.1 The extent of surgery does not influence locoregional recurrence rate 8
1.2.2 The role of radiotherapy in reducing locoregional recurrence rate 9
1.2.3 Tumour biology and locoregional recurrence 9
1.2.4 Identification of the known risk factors for locoregional recurrence and evaluation of initial cancer management 10
1.3 Does the type of surgery performed for initial breast cancer affect prognosis in patients diagnosed with locoregional recurrence? 11
1.4 Definition of locoregional recurrence as true recurrence versus new primary 12
1.5 Uncertainties in the treatment of locoregional recurrence 13
1.5.1 Surgery- repeat breast conserving surgery vs. mastectomy 13
1.5.2 Surgery to the axilla 13
1.5.3 Management of patients presenting with locoregional recurrence with distant metastasis 14
1.5.4 Adjuvant therapy options 14
2.1 Study design 15
2.2 Aims 15
2.3 Objectives 15
2.4 Study endpoints 17
2.4.1 Primary endpoint: 17
2.4.2 Secondary endpoint: 17
3. Definitions 17
4. Methods 17
4.1 National practice questionnaire 18
4.2 National prospective cohort study 18
4.2.1 Patient recruitment 19
4.2.2 Prospective data entry 20
4.3 Evaluation of the initial cancer management 20
4.4 Oncological outcome *evaluation* 21
4.5 Patient consent for future access to archival tissue 21
4.6 Patient inclusion and exclusion criteria 22

4.6.1 Inclusion criteria 22
4.6.2 Exclusion criteria 22
5. Data collection 23
6. Data validation and quality assurance 29
7. Data management and storage 29
7.1 Source data 30
7.2 Access to data 31
7.3 Data recording and record keeping 31
8. Sample size and data analysis 32
9. Publication and authorship policy 33
9.1 Named authors 34
9.2 Citable collaborators 34
9.3 Acknowledged collaborators 35
10. Research Governance 35
10.1 Ethical approval 36
10.2 Informed consent 36
10.3 Study reporting 37
10.4 Patient confidentiality 37
10.5 Archiving 37
10.6 Insurance 37
11. Public and Patient Involvement 37
12. Study Management 38
13. List of participating units 38
14. References 40
15. Appendix 44
MARECA study flowchart 44
MARECA study National Practice Questionnaire on management of breast cancer locoregional recurrence 44
MARECA study Gantt chart 51

1. Background

1.1 The current national status

Breast cancer is diagnosed in approximately 55,000 women per year in the UK (2015-2017; Cancer Research UK[1]) and 5 year survival for all breast cancer patients is favourable at 86.6% as a result of advances in systemic treatment and implementation of the NHS breast screening programme[2]. However, despite this high survival rate, a proportion of patients continue to return to the breast clinic due to cancer recurrence within the conserved breast, ipsilateral skin or chest wall following mastectomy, or in the ipsilateral axillary, supraclavicular, infraclavicular or internal mammary lymph nodes. These cancer recurrences are collected termed locoregional recurrence (LRR). Reflecting the improved cancer treatments, LRR rates are declining. A population based study in Netherlands[3] followed up 1143 patients between 1988 and 2010, and demonstrated that the 5 year local recurrence rate had fallen from 9.8% to 3.3% (comparison of patients diagnosed in 1988-1998 versus 2006-2010). However, recurrences can occur at any time after the original cancer treatment, and a 10 year cumulative LRR incidence of 8% has been reported by a registry-based study in Germany, who followed up patients diagnosed with breast cancer between 1999 and 2009[4]. In the UK, patients who are diagnosed with LRR should be entered into the National Cancer Outcome and Services Dataset (COSD) and to the Cancer Waiting Time (CWT) treatment dataset. However, the reliability of the UK national cancer registries in capturing data about patients diagnosed with LRR requires evaluation as it may be under reported. The 2020 annual report of the National Audit of Breast Cancer in Older Patients (NABCOP) highlights this issue[5]. This audit analysed data from existing routine data sources such as COSD. The 2020 NABCOP annual report determined that for women who died from breast cancer, a high proportion of these patients did not have records registering prior breast cancer recurrence.

In 2012 the National Cancer Registration and Analysis Service (NCRAS) and the National Cancer Intelligence Network (NCIN) reported a pilot audit project for patients diagnosed with recurrent and metastatic breast cancer[6]. Fifteen UK breast units (out of 144) participated for 6 months in 2011. They identified 137 patients with LRR only and 114 patients with both locoregional and distant recurrences. However, this project did not investigate associated patient and tumour characteristics or evaluate the patient's initial cancer treatment. Furthermore, there was a lack of detailed analysis of treatments received by the patients diagnosed with LRR or evaluation of any variation in patient management between

participating units. Most importantly, these patients were not followed up to determine survival outcome.

Reflecting this lack of data, there is no current UK specific guideline on how breast cancer patients with LRR should be managed with little reliable data on the rate of LRR in the UK. The American National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology[7] (BINV-19) provides recommendation as to how patients with LRR should be managed in terms of staging investigations to detect for any presence of distant metastasis, type of LRR resection surgery, management of the axilla, and types of adjuvant treatments to be offered. However, reflecting the relative lack of research in this area, the guideline acknowledges uncertainties in terms of optimal axillary management, the role of LRR resection in the presence of distant metastasis, and as to which staging investigation should be utilised. Multidisciplinary approach is advocated to optimise patient outcome. However, further research is needed to gather data on tumour characteristics and treatment details of the initial and recurrent cancer, which will enable treatment recommendation for LRR to be tailored for each patient in order to achieve optimal outcome.

The 2012 NCIN pilot project demonstrated that the number of patients diagnosed with LRR in each UK breast unit per year are relatively small. Therefore, a national collaborative approach is required. Given the concerns about under-reporting of breast cancer LRR to the UK national cancer registries, retrospective analysis using existing routine data source (e.g. Hospital Episode Statistics) is unlikely to provide data on patient management that is reflective of current national practice. More recently, the national breast surgery research collaboratives have become well-established in the UK and have the capacity to generate a meaningful dataset that is able to describe the current national practice [8-11], which will allow identification of risk factors for LRR as well as current treatment pathways and outcomes.

1.2 Known risk factors for locoregional recurrence

1.2.1 The extent of surgery does not influence locoregional recurrence rate

Multiple studies have examined potential factors which influence the risk of patients developing LRR. As would be expected, patients who at primary diagnosis present with a larger primary tumour and nodal metastatic involvement[12] are at higher risk of LRR. The aim of breast cancer surgery is to resect the tumour with clear margins (i.e. with no tumour at the cut surface). Depending upon the primary tumour size to breast volume ratio, patients are offered breast conserving surgery (BCS) or mastectomy with or without breast reconstruction. This is based on historic randomised control trial data (patients recruited from 1973 and 1980), which showed no difference in long term survival (breast cancer specific and overall survival) for patients who were treated with BCS and whole breast radiotherapy (WBRT) versus mastectomy[13]. 20 year follow up of these patients demonstrated higher crude cumulative local recurrence incidence for patients who received BCS and WBRT versus mastectomy (8.8% versus 2.3%). However, with improved modern therapy, the rate of LRR after BCS and WRBT has fallen considerably with contemporary reported 5 year LRR rates ranging from 2 to 4%[3, 14, 15]. This rate remained stable at 5% at 10 years as reported Bosma et al, who followed up 8485 patients treated with BCS and WBRT at the Netherlands Cancer Institute[14]. Furthermore, analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) randomised clinical trials showed that for patients with large cancers (>5cm), the 10 year cumulative incidence of LRR was 7.1% for patients who were treated with mastectomy[16]. Therefore, the extent of surgery does not significantly influence LRR rate with no differences observed in long term patient survival.

For patients who undergo BCS and WBRT, achieving clear margin reduces local recurrence rate. However, achieving a wider margin width does not influence local recurrence rate. Houssami et al carried out a meta-analysis of over 28,000 patients and demonstrated that margin widths of 1, 2, or 5mm did not affect local recurrence rates [17]. However, the relative risk of developing a local recurrence was 2.44 for involved versus clear margins. Similarly, a Danish cohort study of 11,900 patients determined that having an involved margin was associated with more than twofold risk of local recurrence for patients who had undergone BCS for invasive cancer[18].

1.2.2 The role of radiotherapy in reducing locoregional recurrence rate

Radiotherapy is a key adjuvant treatment that reduces the risk of local recurrence[19] after BCS. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis has demonstrated that WBRT after BCS halves the rate at which recurrences (combined analysis of locoregional and distant metastasis) occur and reduces breast cancer death rate by about a sixth in the long term[19]. Additional studies have demonstrated that the addition of a radiotherapy boost to the tumour bed results in a further reduction in the local recurrence rate for young patients with high grade invasive cancer[20]. Partial breast radiotherapy is non-inferior to WBRT in older patients with early breast cancer in terms of achieving local control[21]. The PRIME II trial concluded that omission of WBRT may be considered for older patients (over 65 years old) with low risk, oestrogen receptor (ER) positive breast cancer after BCS given the modest effect of WBRT in reducing local recurrence risk in this patient group[22]. Therefore, whether patients go on to receive radiotherapy after BCS, as well as the type and regimen, may be individualised according to both patient and tumour factors.

Radiotherapy is also beneficial in patients with high recurrence risk (T3-4, N1-3) disease who undergo mastectomy. Radiotherapy to the chest wall +/- supraclavicular fossa has been shown to reduce LRR and breast cancer mortality even in patients with modest axillary lymph node burden (i.e. one to three nodes) who had received additional systemic therapy[23].

1.2.3 Tumour biology and locoregional recurrence

Tumour biology is a key determinant of which patients are at risk of developing LRR. Patients with HER2 positive and triple negative breast cancers are at higher risk of developing LRR[24]. These patients are therefore treated with chemotherapy, which reduces the risk of LRR[25]. A study by Arvold et al determined 5 year local recurrence rates for 1434 patients who were treated with BCS. They demonstrated that local recurrence rates differed according to biological subtypes. Patients with ER positive and HER2 negative luminal breast cancers had particularly low 5 year local recurrence rates of 0.8% and 2.3% (luminal A and luminal B) respectively. However, patients with HER2 positive and triple negative breast cancers had higher 5 year local recurrence rates of 10.8% and 6.7% respectively. It is worth noting that this study included patients from 1997 to 2006 with patients who did not receive Trastuzumab[26], an effective modern targeted therapy for patients with HER2 positive cancer. A study by Kiess et al showed that the addition of Trastuzumab results in a

significant reduction in LRR rates for patients with HER2 positive cancer[27]. Patients with ER positive and HER2 negative breast cancers are offered endocrine therapy which reduces the risks of LRR and distant metastasis, with subsequent survival benefits[28]. Patients with ER positive HER2 negative primary breast cancers may also be eligible for genomic tests (e.g. Oncotype Dx and MammaPrint), which predicts the individual patient's recurrence risk, including the risk of LRR[29]. Patients who are deemed to have higher risk of recurrence are therefore offered chemotherapy in addition to endocrine therapy[30].

For patients with triple negative breast cancer, no targeted therapy is available for clinical use in the non-metastatic setting and a recent systemic review has demonstrated that patients in this subgroup have the highest rate of LRR at 5 years of 7.4% despite receiving chemotherapy[31]. A study by Radosa et al analysed clinicopathological characteristics and treatments received by 1930 patients with triple negative breast cancer. Their study findings showed that patient age at diagnosis, as well as the type of surgery received (BCS versus mastectomy) did not influence local recurrence rates[32].

Other biological features of the primary tumour also increase the risk of LRR. Rezai et al demonstrated that tumour grading influences the risk of local recurrence. They demonstrated an incremental increase in 5 year local recurrence rates of 1% for grade 1, 2.5% for grade 2, and 7% for grade 3 tumours[33]. The presence of lymphovascular invasion (LVI) also increases the risk of LRR[34]. Therefore, for patients diagnosed with LRR, the clinicopathological and biological features of the original cancer can be evaluated to identify for the presence of these risk factors for LRR.

1.2.4 Identification of the known risk factors for locoregional recurrence and evaluation of initial cancer management

Clinicians may use the above well-defined risk factors to estimate the risk of LRR and tailor the patient's treatment accordingly. Despite this, minority of patients continue to develop LRR. For this study, we will evaluate initial surgical treatment, clinicopathological data, and the patterns of initial adjuvant treatment received. This can then be compared against the UK best practice guidelines[35] as stated by the National Institute for Health and Care Excellence (NICE) to understand why these patients may have developed LRR.

1.3 Does the type of surgery performed for initial breast cancer affect prognosis in patients diagnosed with locoregional recurrence?

The EBCTCG carried out a meta-analysis of 17 randomised trials of radiotherapy versus no radiotherapy in patients treated with BCS, which included patients with both node positive and negative breast cancer. They demonstrated that following BCS and radiotherapy, one breast cancer death was avoided at 15 years for every four recurrences prevented at 10 years. This suggests that following BCS and radiotherapy, three out of four patients with LRR can be treated successfully[19]. In contrast, a further EBCTCG meta-analysis studying the effect of radiotherapy after mastectomy demonstrated that one breast cancer death was avoided at 20 years for every 1.5 recurrences prevented at 10 years[23]. Therefore, after mastectomy and radiotherapy, only one out of three patients diagnosed with LRR can be treated successfully. However, patients included in the latter meta-analysis only included patients with node positive disease, which may explain the observed difference in patient outcome.

Local recurrence after BCS is thought to be due to the growth of previously undetected microscopic multifocal or multicentric tumour foci, which may present on screening mammograms and may therefore be detected early with better subsequent prognosis. In contrast, local recurrence after mastectomy presents as subcutaneous nodules on the chest wall with dermal lymphatic involvement, which may be associated with worse prognosis.

Therefore, further research is required in patients newly diagnosed with LRR to determine whether their prognosis differs according to the type of cancer resection surgery (BCS and radiotherapy versus mastectomy) performed for the initial cancer. This has potential clinical utility as knowing the likely prognosis of the patient diagnosed with LRR will enable their treatments to be tailored accordingly to ensure adequate treatment, whilst avoiding over-treatment. Previous single centre retrospective cohort studies examined consecutive number of patients who presented with newly diagnosed LRR. They found similar distribution in terms of the type of surgery received for the initial cancer (60% BCS and radiotherapy versus 40% mastectomy [36, 37]). These findings support the feasibility of designing an appropriately powered study to examine the prognostic effect of initial breast cancer surgery on patients diagnosed with LRR without distant metastasis. Previous studies have reported conflicting findings with results from the two European randomised trials (patients recruited between 1980 and 1989) showing similar 5 year survival rates of 58% versus 59% for

patients who initially received mastectomy versus BCS[38]. However, a more contemporary study (patients recruited from 1970 to 2008) by Shenouda et al[39] demonstrated that patients diagnosed with LRR who initially received BCS with radiotherapy had better prognosis than those patients who initially received mastectomy (5 year distant metastasis-free survival of 84% versus 60%, with 5 year overall survival of 81% versus 61%). This finding was not influenced by the patient's nodal status.

1.4 Definition of locoregional recurrence as true recurrence versus new primary

When patients are diagnosed with a LRR, there can be uncertainty as to whether this is a true recurrence (TR) or a new primary (NP) breast cancer. Currently there is no standardised classification system and therefore various definitions have been reported in the literature[40].

True recurrence may be defined as cancers with a similar molecular receptor profile (ER/PR/HER2) and histological subtype (Ductal/Lobular/ductal carcinoma in situ) when compared to the originally treated cancer AND for patients who have had previous ipsilateral BCS, the tumour may be classified as TR if the recurrence location is in the same region as the original tumour[41]. Some have reported a 2 or 3 cm distance between the previous operation site and the new lesion as a cut off between a TR and a NP[42, 43] in patients who have previous received BCS. Others have stated that a NP by definition should be accompanied by an in situ component of the lesion[44, 45]. Given the wide range of definitions used, this can result in misclassification of a TR from a NP. This has clinical implications as patients diagnosed with NP are thought to have a better prognosis when compared to patients diagnosed with a TR[43, 45]. The addition of genomic analysis may in future lead to more precise classification between a TR and a NP. Pan-genomic analysis of paired samples of primary tumour with ipsilateral recurrence has been studied in 22 patients with results suggesting its potential clinical utility[46]. However, further studies with larger sample size are required. Genomic analysis may have potential limitations as clonal selection and tumour evolution could lead to the development of recurrent tumour which does not have identical biology when compared to the original tumour. For this study, we will aim to use the existing clinical classification systems and obtain optional patient consent to access archival tissue from both the primary cancer and local recurrence. This would enable

a future translational study to be developed which will compare the clinical and genomic classifications against patient survival outcome.

1.5 Uncertainties in the treatment of locoregional recurrence

For patients who present with LRR, their locoregional and systemic treatment options are variable and are dependent on clinical presentation, previous treatment received for the initial breast cancer, the patient's wishes, and unit practice. Therefore, there is clinical uncertainty with regards to what constitutes optimal management. This study will therefore document the various treatments received by these patients and follow their oncological outcome.

1.5.1 Surgery- repeat breast conserving surgery vs. mastectomy

For patients who have had previous BCS +/- radiotherapy, surgical management of LRR includes completion mastectomy +/- immediate breast reconstruction, or repeat BCS in a previously conserved breast[47]. This latter surgical approach is adopted selectively[48, 49] and there is evidence emerging to show that patients who have repeat BCS have equivalent oncological outcome to these patients who undergo mastectomy in selected patients[50]. If patients are receiving repeat BCS in an irradiated breast, we also need to examine the potential factors that influence this decision making and the subsequent oncological outcome. A notable study by Gentilini and colleagues suggests that patients most suitable for repeat BCS are those who present with a small recurrent tumour with a longer time interval between the original and the recurrent cancer diagnosis[51].

1.5.2 Surgery to the axilla

When patients are diagnosed with a local recurrence in a previously conserved breast, surgery for axillary staging in the form of repeat sentinel lymph node biopsy (SLNB) can be challenging due to aberrant lymphatic drainage. Therefore, there is a lower success rate of re-identifying a SLN in this setting. A recent systematic review[52] has shown that repeat SLNB was successful for 64% of patients with a high negative predictive value of 96.5%. However, the prognostic impact of the results from the repeat SLNB remains unclear[53]. Therefore, collecting information about the methods of SLN re-localisation, the success rate of SLN re-identification and its long term prognostic impact at national level will be valuable towards setting guidelines and to evaluate whether the information gathered from the repeat SLNB has any impact on further adjuvant treatment decision making.

1.5.3 Management of patients presenting with locoregional recurrence with distant metastasis

There are further management options emerging for patients who present with LRR and distant metastasis. Traditionally these patients were not considered for surgical resection of the LRR, except in cases where surgery would provide palliation (e.g. where a fungating tumour was bleeding, painful or difficult to manage with dressings). However, small numbers of patients are currently being managed with surgical resection of the LRR in the presence of distant metastatic disease[54]. This is especially relevant with advances in systemic therapy (e.g. anti-HER2 therapies and CDK inhibitors), which may enable some patients with metastatic breast cancers to undergo LRR resection if deemed to have good response to systemic therapy or for local control with palliative intent. Breast surgery to the primary cancer in the presence of distant metastasis has been evaluated in Austria (ABCSG-28 POSYTIVE trial[54]), India[55] and Turkey (MF07-01 trial[56]) with conflicting survival benefit observed. Currently in the UK, it is not known how many patients are undergoing surgery for LRR in the presence of distant metastasis. Therefore, a national database to record their management and survival outcomes would be of value and can be compared against the patients with LRR without distant metastasis.

1.5.4 Adjuvant therapy options

Cancer recurrence may be due to survival and proliferation of clones that are resistant to a range of adjuvant therapies. Therefore, it would be of interest to examine the choice of endocrine and/or chemotherapy in patients with LRR. The CALOR trial demonstrated that patients with ER- (but not ER+) locally recurrent cancer benefited from further chemotherapy[57]. This randomised control trial demonstrated improved 5 year disease free survival (69% versus 57%) and overall survival (88% versus 76%) for patients who received chemotherapy after LRR resection surgery. There is also an increasing role for partial breast radiotherapy in patients treated with repeat BCS who have had previous BCS and radiotherapy[58]. Compared to treatment for primary breast cancer, there is a relative lack of clinical trial data on the efficacy of further adjuvant systemic therapy in patients diagnosed with LRR. The MARECA study will gather data on the type of adjuvant treatments currently used to treat patients diagnosed with LRR in the UK.

Given the complexity mentioned so far in the multidisciplinary management of patients with LRR, there is a need to examine long term oncological outcome and determine optimal patient management. The current literature reporting survival outcome for patients diagnosed with LRR are mostly based on single institution retrospective studies with

significantly different reported patient outcomes; a 5 year disease free survival (DFS) rate of 48 to 67% has been reported, and an equivalent overall survival (OS) rate of 61 to 82% has been reported[59]. Furthermore, these published studies are over 10 years old, reflecting the need to perform a prospective study to determine patient outcome, which reflects modern breast cancer treatment.

One of the key aim of the MARECA study will be to identify which patient groups are at most risk of further LRR, distant metastasis, and subsequent mortality after their treatment of LRR. A notable study in 2009 reported OS rates for patients with node negative cancer who were treated by BCS and WBRT as part of the NSABP protocols of node negative breast cancer[60]. They reported worse OS outcome in patients who presented with recurrences in the regional lymph nodes, as opposed to recurrences in the conserved breast (5 year OS of 34.9% versus 76.6% respectively). In addition, shorter interval time between the initial and recurrent cancer diagnosis has been identified as a poor prognostic factor for patients diagnosed with LRR[61]. By evaluating the tumour characteristics and treatment patterns of the initial and recurrent cancer, MARECA study will aim to identify other predictive prognostic factors for patients diagnosed with LRR. This will in turn guide clinicians with an aim of optimising patient management and improve treatment outcomes.

2. Aims and Objectives

2.1 Study design

The MARECA study is a prospective, observational, multicentre, longitudinal cohort study.

2.2 Aims

The MARECA study will determine the frequency, current management and prognosis of patients diagnosed with breast cancer locoregional recurrence in the UK with the aim of establishing best practice and informing future national guidelines.

2.3 Objectives

1. To carry out a national survey of UK breast units in order to establish the current stated practice of breast MDTs regarding the management of patients with locoregional recurrence and identify any potential geographical variations.

2. To establish a prospective cohort of breast cancer patients diagnosed with locoregional recurrence +/- distant metastasis in order to:

i) Describe current management including:
   - Use of radiological staging investigations and the proportion of patients found to have distant metastasis (DM) at presentation.
   - Surgical management including the use of repeat BCS and SLNB.
   - Use of systemic therapies and radiotherapy used to treat locoregional recurrence.

ii) Investigate risk factors associated with LRR development including those related to the primary breast cancer and its management.

iii) Determine the following oncological outcome at 3 and 5 years, and evaluate prognostic factors;

   -Disease Free Survival (DFS) for patients diagnosed with LRR without associated distant metastasis at presentation.

   -Progression Free Survival (PFS) for patients diagnosed with LRR with associated distant metastasis at presentation.

   -Overall Survival (OS) for patients diagnosed with LRR with or without associated distant metastasis at presentation.

iv) Stratify LRR as a true recurrence (TR) or a new primary (NP) breast cancer using clinical classification systems and explore if this distinction affects oncological outcomes.

3. To determine the feasibility of designing a future potential translational study. Patients enrolled in the study will be invited to provide optional consent for permission to access archival tissue samples (or slides) of both the primary cancer and the locoregional recurrence. This would permit comparison of clinical and genomic classification of locoregional recurrences (true recurrence or new primary) against patient survival outcome.

2.4 Study endpoints

2.4.1 Primary endpoint:

DFS following LRR resection in patients who present without distant metastasis, stratified according to the type of surgery performed for the primary breast cancer (BCS and radiotherapy vs. mastectomy).

2.4.2 Secondary endpoint:

-PFS in patients who present with LRR with distant metastasis.

-OS in patients with LRR +/- DM at presentation.

3. Definitions

For the purpose of this study, LRR is defined as diagnosis of invasive breast cancer or ductal carcinoma in situ in the ipsilateral breast (if applicable)/skin/chest wall/regional nodes (axilla/internal mammary/supraclavicular/infraclavicular) following previous breast cancer treatment with curative intent.

4. Methods

This is a prospective observational multicentre longitudinal cohort study. This will be a national research study in collaboration with the Association of Breast Surgery (ABS) Academic and Research committee, the Mammary Fold Academic and Research Collaborative (MFAC) committee, and the UK Breast Cancer Trainees Research Collaborative Group (BCTRCG).

The study will have 3 main phases;

1. National practice questionnaire on current management of patients diagnosed with LRR by breast MDTs across UK.

2. Development of a national prospective cohort of patients newly diagnosed with LRR +/- DM in order to document management details for each patient with respect to their original and recurrent cancer.

3. Evaluating oncological outcomes of the study cohort at 3 and 5 years by collation and analysis of the data submitted from the participating centres.

4.1 National practice questionnaire

The MARECA study National Practice Questionnaire (NPQ) will consist of scenario-based questions (see Appendix) for the breast cancer multidisciplinary teams (MDTs) at the participating centres. It aims to document the current stated practice of breast cancer LRR management, and is designed to capture data on practice variations and areas of uncertainty in patient management. A trainee lead (specialty training registrar or specialty doctor) at each centre will be identified (via MFAC and BCTRCG) who will be asked to complete the questionnaire at the weekly breast MDT meeting and hence ensuring maximal input from all MDT members. The trainee lead will document the number of participants present at the MDT meeting, as well as the MDT composition (e.g. breast surgeons, oncologists, histopathologists, and radiologists). Trainee led research collaboratives have been successful in gaining high response rates for such national practice questionnaires (e.g. iBRA study[62]). The NPQ will be available online (www.surveymonkey.com) to enable ease of completion by each MDT and will be compatible with the current remote pattern of MDT meeting function (as a result of the coronavirus pandemic).

The NPQ will be completed by the participating sites between February and August 2021 prior to the commencement of the prospective cohort study. It has been developed to explore each MDT approach on the following themes;

- Pre-operative investigations.
- The type of breast and axillary surgery offered based on common clinical scenarios.
- Potential factors influencing the decision to offer repeat BCS.
- The type of systemic therapy and radiotherapy offered to treat LRR.

4.2 National prospective cohort study

All UK breast units will be invited to participate through ABS, MFAC, and BCTRCG. The study will also be included in the iBRA-NET research portfolio (https://www.ibra-net.com/mareca). The study will be rolled out nationally for 24 months from November 2021 with the aim of recruiting consecutive eligible patients diagnosed with LRR +/- DM in at least 50 participating UK breast units. The study has been designed to collect information about tumour characteristics and treatment details for the patient's original and recurrent cancer. The study aim is to determine long term prognosis in patients diagnosed with LRR, which will require patient consent. Therefore, ethical approval will be (www.Hra-

decisiontools.org.uk/research) sought to include all participating centres via the Integrated Research Application System (IRAS).

A unit trainee lead will act as an associate principal investigator (pending application outcome for NIHR CRN portfolio status), who will be supervised by the principal investigator (PI, either consultant breast surgeon or oncologist) for each unit. For units without trainees, a designated member of the Clinical Research Network (CRN) research team will act in this role. The PIs will therefore have support in order to recruit and consent eligible patients to the study, as well as complete the Case Report Form (CRF) in order to determine;

- Modality of radiological staging investigations used and determination of the rate of detection of distant metastasis.
- Proportion of patients undergoing repeat breast conserving surgery for in breast recurrence.
- Proportion of patients undergoing repeat sentinel lymph node biopsy, techniques used, and their success rate in terms of sentinel lymph node re-identification.
- Adjuvant treatment modalities used to treat the LRR.
- Proportion of patients undergoing breast surgery for locoregional recurrence in the presence of distant metastasis.

4.2.1 Patient recruitment

Eligible patients (see section 4.6) will be identified at the breast MDT meeting or in breast and oncology clinics by the clinicians directly involved in the patient's care. As part of the direct clinical team, the trainee lead, an appropriately trained member of the team (including research nurses or trials assistants, as per the delegation log), or consultant breast surgeon or oncologist at each unit will discuss the option of study participation with the patient at the clinic and provide a study patient information sheet. This is in accordance with Good Clinical Practice (GCP) guidelines and will have been documented and approved by the Principal Investigator on the delegation log. Identified patients may also be invited to participate using the approved invite letter which can be posted to patients along with the PIS. This will be used to improve the patient identification/approach pathway by providing an additional opportunity for patients to participate in the study. The Patient Invitation Letter v1.0 dated 25 May 2022 incorporates a sentence for the research nurse to be allowed to contact the patient to check if the patient is interested in the study.

Patients will be given sufficient time to consider the study information and ask any questions they may have about participation. For patients who agree to participate in the study, they will sign and date the latest approved version of the informed consent form enabling the study specific data collection to proceed. Written consent can be taken by the Principal Investigator, a trainee lead or an appropriately trained member of the team (this may include research nurses or trials assistants). The completion of the consent form may occur during the patient's scheduled hospital visits so not to incur additional hospital visits as a result of agreeing to participate in the study. To reduce burden, patients can also be offered the option to consent the same day as approach if they feel they have had sufficient time to consider the study and the HCP taking consent if happy that they have full understanding. Patients may also consent by post following invite in person or having been approached by the approved invite letter and accompanying PIS.

4.2.2 Prospective data entry

The trainee lead, a designated member of the CRN research team, or consultant breast surgeon or oncologist will be responsible for the prospective data collection which will involve recording patient data that is routinely collected as part of standard clinical practice. The data collection will involve accessing the hospital electronic records or patients' notes to document details about the management of the initial and recurrent cancer (see section 5). This will include reviewing the patient's clinic letters, imaging and pathology reports, operation notes, MDT meeting recommendations, and any other relevant information relating to the patient's cancer treatment. Data will be recorded in a pseudonymised format using a unique alphanumeric study identification number on a secure web-based database (REDCap) designed by Vanderbilt University[63, 64] (http://www.projectredcap.org/). Each participating unit will have individual access to add data to the central REDCap database for the study. The data from each unit will have a unique designated ID, which will be used as a prefix for the patient ID (e.g. SJUH01).

4.3 Evaluation of the initial cancer management

Data collection about the original cancer management will aim to identify known risk factors for LRR (see section 1.2). This will involve examination of the tumour characteristic and the treatment received for the initial cancer. NICE guideline[35] on 'early and locally advanced breast cancer: diagnosis and management (NG 101)' provides recommendations about which patients should be offered particular adjuvant treatments based on the tumour

characteristics and the surgery performed. Therefore, the receipt of, as well as compliance with, the recommended adjuvant treatment will be explored with regards to the management of the patient's original cancer.

4.4 Oncological outcome *evaluation*

Given that trainees rotate regularly to different hospitals within their respective deaneries, the latter phase of the study examining oncological outcomes at 3 and 5 years will be led by the consultant principal investigators with support from the local research nurses and clinical trial assistants. The following information will be sought from the participating units;

Oncological outcome dataset at 3 and 5 years after LRR diagnosis

-Patient Alive? (Yes/No)

-If No, was it related to breast cancer? (Yes/No; If No what was the cause of death)

-Date of death

-Any further LRR +/- distant metastasis

-Date of further LRR

-Date of distant metastasis

Collection of the above data will enable determination of the patient's disease free survival (DFS), disease specific survival (DSS), progression free survival (PFS), and overall survival (OS). We would not anticipate direct patient contact for study purpose during this follow up period. In cases where the required information is missing or unclear, the research team may contact the patient or their General Practitioner via telephone.

4.5 Patient consent for future access to archival tissue

Patients participating in the MARECA study will also be able to provide optional consent to donate their archived cancer tissue samples or slides for a potential research project in line with one of the study objectives (i.e. to determine the feasibility of designing a future potential translational study). The tissue samples will be pseudonymised. For the present study, participating centres will be not be required to access/process/store/retrieve any tissue sample any differently to current standard of routine clinical care. Consent for future

tissue sample or slide access will allow examination of the following potential research questions;

-Genomic/transcriptomic/proteomic comparison of archival tumour tissue from the primary cancer with that of the recurrent cancer. This will enable distinction of a new primary cancer from a true recurrence. This will be compared against the current clinical classification to determine if patient prognosis differs.

-Facilitate transfer and storage of these tumour samples in a centralised HTA approved tissue bank for future translational research studies with a focus on identification of biomarkers that predict treatment resistance.

If funding is obtained for the potential follow on translational studies, new ethics, R and D contracts and protocols will be made available to participating units, but patient consent will be retained from this study.

4.6 Patient inclusion and exclusion criteria

4.6.1 Inclusion criteria

- Female or male patients more than 18 years old.Treated for previous unilateral or bilateral breast cancer (invasive cancer including all histological subtypes as well as ductal carcinoma in situ) with curative intent.
- No previous evidence of distant metastatic disease.
- Recently (within the last 6 months) diagnosed with new ipsilateral breast cancer locoregional recurrence (biopsy proven invasive cancer including all histological subtypes or ductal carcinoma in situ) +/- distant metastasis.
- Able to provide written informed consent.
- A *minimum of 3 months interval* between the resection surgery for the original cancer and the diagnosis of locoregional recurrence. There will be *no maximum interval time period*.

4.6.2 Exclusion criteria

- Patients where the new breast cancer diagnosis is in the contralateral breast.
- For patients who present with new bilateral breast cancer, the side with no previous cancer will be excluded.

- Patients diagnosed with distant metastatic disease with no evidence of LRR.
- Patients diagnosed with angiosarcoma.
- Patients with previous history of non-breast cancer treatment that was non-curative in intent
- Patients who have had previous ipsilateral surgery for atypia, benign conditions, or phyllodes tumour and other breast sarcomas AND no previous ipsilateral primary breast cancer resection.
- Patients under 18 years old.
- Patients lacking capacity to provide written informed consent.

5. Data collection

The following dataset will be collected prospectively during the 24 months patient recruitment phase. Data regarding the management of LRR will be collected prospectively as the patient's care progresses.

1. Patient demographics (at the time of LRR diagnosis) collected will include;

   1.1 Centre name and ID
   1.2 Age (years)
   1.3 Current menopausal status (pre-menopausal, post-menopausal, peri-menopausal)
   1.4 BMI
   1.5 Smoking status (non-smoker, ex-smoker, current smoker)
   1.6 Patient performance status (0 to 4; based on Eastern Cooperative Oncology Group score)
   1.7 Family history risk as defined by NICE guideline; CG164[65] (unknown / population risk / moderate risk / high risk / BRCA mutation positive / other known germline breast cancer susceptibility gene pathogenic mutation- e.g. TP53 gene mutation)

2. Treatment detail about the original breast cancer

Surgery

   2.1 Date of original breast cancer surgery
   2.2 Screening or symptomatic diagnosis
   2.3 Age at original diagnosis

2.4 Type of breast surgery (none / breast conserving surgery / mastectomy + immediate breast reconstruction / mastectomy and delayed reconstruction/ mastectomy with no reconstruction)

2.5 If breast conserving surgery was performed for invasive lobular cancer, was MRI performed (Yes/No/Not applicable)

2.6 What was the original tumour location (upper inner quadrant / upper outer quadrant / lower inner quadrant / lower outer quadrant / subareolar or central)

2.7 Type of axillary surgery (none / sentinel lymph node biopsy / axillary node clearance / axillary node sampling / targeted axillary dissection)

2.8 If sentinel lymph node biopsy, method of localisation (dual technique with blue dye and radioisotope / radioisotope alone / blue dye alone / other methods)

2.9 Was the original breast cancer inflammatory breast cancer (Yes/No)

Pathology

2.10 Tumour subtype (invasive ductal / invasive lobular / mixed ductal and lobular / other subtypes / pure ductal carcinoma in situ)

2.11 Tumour grade (1 to 3 for invasive / low to high grade for ductal carcinoma in situ)

2.12 Tumour size (in mm; invasive tumour size, unless DCIS)

2.13 Multifocal or multicentric cancer (Yes/No)

2.14 Lymphovascular invasion (Yes/No)

2.15 Closest radial margin after final surgery (in mm)

2.16 Were anterior or posterior margins close (1mm or less)? If Yes, please state which (anterior / posterior / both) and distance in mm (0,1)

2.17 Number of positive axillary nodes (state macro- or micrometastasis)

2.18 Number of axillary lymph nodes retrieved

2.19 Oestrogen receptor Allred score (ER; 0 to 8; please state if any other scoring system was used and its score; e.g. H-score)

2.20 Progesterone receptor Allred score (PR; 0 to 8; please state if any other scoring system was used and its score; e.g. H-score)

2.21 HER2 receptor status (Positive or negative; please state immunohistochemistry score 0/1+/2+/3+; if 2+ was FISH test done? What was the final HER2 receptor status if FISH test done; positive/negative/not applicable)

2.22 Ki67 test? If Yes, please state %

Adjuvant treatment

2.23 Receipt of radiotherapy after breast conserving surgery or mastectomy (Yes/No/Not applicable)

2.24 If radiotherapy after breast conserving surgery, please state radiotherapy regimen (whole breast radiotherapy; 40 Gy in 15 fractions / whole breast radiotherapy; 27Gy in 5 fractions (hypofractionated) / partial breast radiotherapy / whole breast radiotherapy with boost)

2.25 Radiotherapy to the axilla (Yes/No)

2.26 Supraclavicular fossa radiotherapy (Yes/No)

2.27 Internal mammary node radiotherapy (Yes/No)

2.28 Receipt of adjuvant endocrine therapy (Yes/No)

2.29 If receiving or received endocrine therapy, please state duration received (total number of years)

2.30 Please state first line endocrine therapy (tamoxifen / letrozole / anastrozole / exemestane / ovarian suppression / others; please specify)

2.31 What was the duration of the first line endocrine therapy? Please state number of years

2.32 Please state second line endocrine therapy if applicable (not applicable/ tamoxifen / letrozole / anastrozole / exemestane/ ovarian suppression / others; please specify). Please state the duration in number of years (if applicable)

2.33 Receipt of chemotherapy (Yes/No)

2.34 If received chemotherapy was is adjuvant or neoadjuvant?

2.35 Was an Oncotype Dx or other predictive test used? (Yes/No; If Yes, what test was used and please state the score)

2.36 Please select which chemotherapy agents the patient received (epirubicin / doxorubicin / docetaxel / paclitaxel / cyclophosphamide / carboplatin / capecitabine / others; please state)

2.37 Was chemotherapy stopped early (e.g. due to side effects); Yes/No

2.38 Receipt of anti-HER2 treatment (Yes/No). If Yes, was it trastuzumab (Herceptin) or trastuzumab (Herceptin) and pertuzumab (Perjeta)?

2.39 Receipt of bisphosphonates (Yes/No)

3. Treatment detail about locoregional recurrence

Diagnosis

3.1 Date of diagnosis for LRR

3.2 Screening or symptomatic diagnosis

3.3 Age at diagnosis of LRR

3.4 Tumour subtype (invasive ductal / invasive lobular / mixed ductal and lobular / other subtypes / pure ductal carcinoma in situ)

3.5 If invasive cancer diagnosis, was there associated ductal carcinoma in situ? (Yes/No)

3.6 Tumour grade (1 to 3 for invasive; low to high grade for ductal carcinoma in situ)

3.7 Oestrogen receptor Allred score (ER; 0 to 8; please state if any other scoring system was used and its score; e.g. H-score)

3.8 Progesterone receptor Allred score (PR; 0 to 8; please state if any other scoring system was used and its score; e.g. H-score)

3.9 HER2 receptor status (Positive or negative; please state immunohistochemistry score 0/1+/2+/3+; if 2+ was FISH test done? What was the final HER2 receptor status if FISH test done; positive/negative/not applicable)

3.10 Ki67 test? If Yes, please state %

3.11 If patient had breast conserving surgery for the original cancer, please state the tumour location for the recurrent cancer (upper inner quadrant, upper outer quadrant, lower outer quadrant, lower inner quadrant, subareolar or central)

<u>Investigations</u>

3.12 Please state the site(s) of LRR (breast / skin / chest wall / axilla / internal mammary nodes / supraclavicular nodes / infraclavicular nodes; please select all that applies)

3.13 If breast LRR, what was the maximal tumour size on imaging (in mm)

3.14 Was axilla ultrasound scan performed (Yes/No)

3.15 Was it reported as normal (Yes/No)

3.16 If reported as abnormal, what was the FNA/core biopsy result (C1 to 5 or B1 to 5)

3.17 Was staging investigation performed to investigate for the presence of distant metastasis (Yes/No)

3.18 If staging was performed, what modality was used? Please select from the following options (CT chest/abdomen/pelvis / CT chest/abdomen/pelvis and bone scan / PET CT / Others)

3.19 Did staging investigations reveal any evidence of distant metastasis (Yes/No; if No skip to section to 3.23)

3.20 If evidence of distant metastasis, please state site (bone / brain / liver / lung / other sites; please select all that applies)

3.21 Did the patient undergo surgery in the presence distant metastasis (Yes/No; If no please skip to section 3.39)

3.22 Was any neoadjuvant systemic therapy used for patients with LRR (neoadjuvant chemotherapy / neoadjuvant endocrine therapy / CDK inhibitors / others; please state rationale for neoadjuvant systemic therapy; i.e. curative intent or palliative with downstaging to enable surgery for local control)

Surgery

3.23 Did the patient receive surgery for LRR (Yes/No; if No please skip to section 3.39)

3.24 If the patient did not receive surgery for LRR, please state the reason (LRR unresectable / patient deemed unfit for surgery / patient choice / due to distant metastasis identified on staging scans / commenced on systemic therapy first / other reasons; please specify)

3.25 State the date of surgery for LRR

3.26 What breast surgery was performed (none / simple mastectomy / mastectomy with immediate breast reconstruction (implant or fully autologous or autologous with implant) / mastectomy with deconstruction (taking down of previous reconstruction) / repeat breast conserving surgery / wide local excision of skin flap or chest wall recurrence (please state the method of wound closure; direct closure / skin graft / flap closure)

3.27 What axillary surgery was planned (none / sentinel lymph node biopsy (no previous axillary surgery) / repeat sentinel lymph node biopsy / axillary node sampling / axillary node clearance / targeted axillary dissection / axillary exploration after previous axillary node clearance / others)

3.28 If repeat sentinel lymph node biopsy was performed, what localisation method was utilised (dual technique with blue dye and radioisotope / radioisotope only / blue dye only / others)

3.29 If repeat sentinel lymph node biopsy was performed, was it successful in identifying the sentinel lymph node (i.e. was a ‘hot’ and/or blue lymph node identified?; Yes/No)

3.30 If unsuccessful and no sentinel lymph node was identified during surgery, how did you proceed (no further axillary dissection / axillary node sampling / axillary node clearance)

LRR pathology

3.31 Multifocal or multicentric cancer (Yes/No)

3.32 Lymphovascular invasion (Yes/No)

3.33 Tumour size (invasive size in mm, unless DCIS)

3.34 Closest radial margin (in mm)

3.35 Were anterior or posterior margins close (1mm or less)? If Yes, please state which (anterior / posterior / both) and distance in mm (0,1)

3.36 Number of positive axillary nodes (state macro- or micrometastasis)

3.37 Number of lymph nodes retrieved

Adjuvant treatment for LRR (including further surgery)

3.38 Was further surgery to the breast required (Yes/No). If Yes, please state the type of further breast surgery (re-excision of margins / mastectomy)

3.39 Was further surgery to the axilla required (Yes/No). If Yes, please state the type of further axillary surgery and date (axillary node clearance / sentinel lymph node biopsy/ axillary node sampling)

3.40 Receipt of breast radiotherapy (Yes / No/ not applicable)

3.41 If radiotherapy after breast conserving surgery, please state radiotherapy regimen (whole breast radiotherapy; 40 Gy in 15 fractions / whole breast radiotherapy; 27Gy in 5 fractions (hypofractionated) / partial breast radiotherapy / whole breast radiotherapy with boost)

3.42 Post-mastectomy radiotherapy (Yes/No/ not applicable)

3.43 Radiotherapy to the axilla (Yes/No)

3.44 Supraclavicular fossa radiotherapy (Yes/No)

3.45 Internal mammary node radiotherapy (Yes/No)

3.46 Receipt of endocrine therapy (Yes/No)

3.47 If receiving endocrine therapy, please state the duration recommended at the MDT meeting (number of years)

3.48 What endocrine therapy was the patient prescribed (tamoxifen / letrozole / anastrozole / exemestane/ ovarian suppression / others; please specify)

3.49 Receipt of chemotherapy (Yes/No)

3.50 Please select which chemotherapy agents the patient received (epirubicin / doxorubicin / docetaxel / paclitaxel / cyclophosphamide / carboplatin / capecitabine / others; please state)

3.51 Receipt of anti-HER2 treatment (Yes/No). If Yes, was it trastuzumab (Herceptin) or trastuzumab (Herceptin) and pertuzumab (Perjeta)?

3.52 Receipt of other targeted treatment (Yes/No; if Yes, please specify)

6. Data validation and quality assurance

Data collected on each patient must be recorded by the Principal Investigator, or his/her designee, as accurately and completely as possible. The Principal Investigator is responsible for the timing, completeness, legibility, accuracy and signing of the data entry on REDCap database and the CRF. The Clinical Investigators must allow study staff access to any required background pseudonymised data from hospital records (source data e.g. medical records) on request.

All fields MUST be completed. All data submitted must be verifiable in the source documentation. These may include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the REDCap database and the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographs and correspondence. All documents will be stored in confidential conditions. Any deviation from this must be explained appropriately.

For quality assurance purposes, the Consultant principal investigator at all participating sites will be asked to identify an independent person to validate a proportion of the submitted data. Overall, approximately 5% of the dataset selected at random will be independently validated. If concordance between the number of cases submitted on REDcap and those identified independently is <90%, the Unit's data will be excluded from the analysis. This is consistent with the quality assurance procedure used in other large collaborative audit projects[66].

7. Data management and storage

Data collection will occur in accordance with GCP, Caldicott principles and the General Data Protection Regulation (GDPR) 2018, and will work in line with NHS confidentiality guidelines and codes of conduct. Data for each patient will be pseudonymised using a unique

alphanumeric study identification number. No patient identifiable data will be recorded into the REDCap database and the CRF for the purpose of the study.

Study data will be collected and managed using REDCap electronic data capture tools hosted at University of Manchester and made freely available to research collaboratives in the UK. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. More information about the consortium and system security can be found at http://www.projectredcap.org/.

The local PI will keep a secure record of the RedCap ID with corresponding NHS number (in England Wales), Community Health Index number (in Scotland), or Health and Care number (in Northern Ireland). This is required for the research team at each participating centres (Consultant PI, research nurse, and clinical trial assistants) to access the hospital electronic system at 3 and 5 years after LRR diagnosis to record the oncological outcome as specified in section 4.4.

7.1 Source data

Source documents are where data is first recorded, and from which participants' data are obtained. These will include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the REDCap database or the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data verification will be monitored to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996. Monitoring by the Chief Investigator or authorised authorities will be to ensure

- Sufficient data is recorded to enable accurate linkage between hospital records and CRFs/REDCap database
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit

- Staff working on the trial will meet requirements of the EU Directive

7.2 Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

7.3 Data recording and record keeping

All information collected during the course of the study will be kept strictly confidential. The information governance team (including the trust's Caldicott guardian) at Leeds Teaching Hospitals NHS Trust has reviewed the study protocol, and we have obtained Caldicott approval for the study.

Information will be held securely on paper and electronically at each participating NHS Trusts. All participating sites will comply with all aspects of the Data Protection Act 2018 and operationally this will include:

- consent from patients to record personal details including name, date of birth, address and telephone number, email address, NHS ID and hospital ID
- appropriate storage, restricted access and disposal arrangements for patient personal and clinical details
- consent from patients for access to their medical records by responsible individuals from the research staff, the sponsor, and from regulatory authorities, where it is relevant to trial participation
- Consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.

Data completeness is an integral part of any study. A CONSORT style will be used to monitor data completeness from eligibility screening, approach, study acceptance through to the final follow-up visit. This information will be made available to the study steering group as regular reports. The team will also report the number of:

- Patients screened per month
- Patients approached per month (and reasons why not approached)
- Patients recruited per month
- The number of patients who complete each follow up visit or are lost to follow-up
- The number of patients who complete the trial.

8. Sample size and data analysis

All data analysis will occur centrally and will be led by the steering group. Local collaboratives and hospital trusts will have ownership of their own data and will be able to present it locally if they so wish. Summary statistics will be calculated for each participating Trust and fed back to individual units to allow comparison with national averages and ranges. It is important to note that we cannot determine locoregional recurrence rate for each unit or at national level. We will not have a denominator to determine this rate.

Descriptive summary statistics will be calculated for each outcome and regression analysis used to control for predictive variables. Data will be tested for distribution and differences between groups using unpaired t-tests, Mann-Whitney U tests and Chi squared tests as appropriate. Based on the NCRAS report described in section 1, approximately 250 patients were diagnosed with LRR with or without distant metastasis across 15 UK breast units over 6 months. This data suggests that around 33 patients will be eligible for recruitment over 12 months in each breast unit. This potential sample size has been corroborated from data at Leeds Teaching Hospitals NHS trust (LTHT) where 28 patients met the eligibility criteria (January 2019 to December 2019). This was based on information from the LTHT cancer information team. There are 144 breast units in the UK and at least 50 units so far have agreed to participate in the study. Given the variable number of cancer patients treated per year in these participating units, we would anticipate each unit to recruit 5 to 10 patients over 12 months. Therefore, we would aim to recruit at least 500 patients diagnosed with LRR +/- distant metastasis over 24 months. There are no statistical criteria for stopping the study early as the study is observational in nature examining current UK practice and therefore low risk.

One of the key aim of the study is to determine whether patient prognosis after their LRR diagnosis (without distant metastasis) differs according to the type of breast cancer surgery (mastectomy versus BCS and radiotherapy) for the initial cancer. Based on published studies[36, 37, 39], the distribution of patients presenting with LRR is almost even between mastectomy and BCS for the initial cancer (40% mastectomy and 60% BCS). From these published studies, the 5 year DFS after treatment for LRR has been reported to be approximately 70%[67, 68]. A single centre retrospective study by Shenouda *et al*[39] identified that patients initially treated with BCS and radiotherapy had improved DFS by

approximately 20% as compared to patients initially treated with mastectomy and no radiotherapy (5 year DFS of 80% vs. 60%).

Power calculation was performed to determine sample size in each group (patients treated with mastectomy versus BCS and radiotherapy for the initial cancer), using logistic regression analysis to adjust for other covariates stated in the background section (tumour and nodal staging, molecular receptor profile, and tumour grade). This calculation has determined that the estimated sample size for each group would be 165 patients. Therefore, a subset of 330 patients diagnosed with LRR without distant metastasis will require recruiting to the study to determine whether patient prognosis differs according to the type of breast cancer surgery performed for the initial cancer. This falls well within the minimum patient recruitment target of 500 patients who are diagnosed with LRR +/- distant metastasis.

Kaplan Meier survival analysis will be performed at the two study time points (3 and 5 years after diagnosis of LRR). We will determine DFS/PFS/OS for the study participants. DFS will be determined for patients diagnosed with LRR without associated distant metastasis at presentation who then subsequently undergo LRR resection. PFS will be determined for patients diagnosed with LRR with associated distant metastasis at presentation. OS will be determined for the whole study cohort (i.e. patients diagnosed with LRR with or without associated distant metastasis at presentation). We will perform Cox proportional hazards regression for multivariate analysis and log-rank tests for univariate analysis, including potential prognostic factors as variables of interest.

9. Publication and authorship policy

All presentations and publications will be made on behalf of the MARECA study steering group. The steering group will be responsible for drafting manuscripts and preparing them for publication. Three levels of authorship are proposed based on degree of study participation:

9.1 Named authors

Named authors will be required to meet the International Committee of Medical Journal Editors (ICMJE) criteria (www.icmje.org) for authorship based on the following four criteria:

1. Substantial contribution to the conception or design of the work; or the acquisition, analysis or interpretation of the data for the work and

2. Drafting the work or revising it critically for important intellectual content and

3. Final approval of the version to be published and

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The ICMJE states 'when submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript and MEDLINE lists authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.'

All citable collaborators will therefore be listed at the end of the paper and their roles identified.

9.2 Citable collaborators

Citable collaborators will have made a considerable contribution to the study, but will not have met the ICMJE criteria for authorship (non-author contributors). These will include trainee or consultant leads at each centre and other trainees or team members (including consultant surgeons or oncologists, clinical nurse specialists or research nurses) who have recruited at least 5 patients to the study. Recruitment in this context includes the submission of ***at least five completed data sets***. Judgement may be used to determine participation according to local centre practice. Unit leads will be asked to provide details of their local

team and whether individuals fulfil the criteria for citable or acknowledged collaborator status.

9.3 Acknowledged collaborators

Acknowledged collaborators will include consultant surgeons or oncologists who contributed patients to the study, but did not personally collect data or recruit patients and trainees who have made a lesser contribution to patient recruitment and data collection than that required for citable collaborator status. Trainees who are acknowledged contributors will also receive a certificate of participation for inclusion in their portfolios.

The final reports will be prepared in accordance with the STROBE(19) (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

10. Research Governance

This is a prospective observational multicentre longitudinal cohort study to evaluate potential variation in treatment for patients diagnosed with LRR +/- DM. The patient's clinical care and management will not be affected by participating in the study given its non-randomised nature. Given the relatively small number of patients diagnosed with LRR in each UK breast unit, a national approach is required to examine current practice and examine long term oncological outcome in order to set national guideline and optimally manage this group of patients. Patients who consent to the study will give permission for their original and current cancer treatment details and outcome to be examined for research purpose. Patients will be free to withdraw their consent for the study at any time. In this circumstance, data up until the point of withdrawal will be used unless patients request removal of their data from the study database.

The feasibility of the recruitment process will be evaluated by using the screening logs, eligibility and consent processes. If reasons for ineligibility and non-participation have been provided, these will be summarised. Follow up retention, including the number of participants who withdraw and any reasons for withdrawal will be described.

There is no pre-defined safety end-point for this study. However, any adverse events which occur as a result of normal care will be reported to the study team. The study has been designed to avoid burden to the patient such as a need for extra hospital visits. This also

applies to the patients who consent for future access to tissue samples or slides. The stored tissue samples or slides will form part of routine clinical practice in the pathology laboratory (i.e. archival storage of FFPE tumour blocks as opposed to collection of fresh tissue that requires different storage technique with additional associated costs) and patients will not be asked to undergo any extra procedures for tissue sample access.

10.1 Ethical approval

Research Ethics Committee approval will be obtained for all sites registered for the study. The Investigator will submit and, where necessary, obtain approval from the above parties for any substantial amendments to the original approved documents. Patient consent will permit linkage of pseudonymised trial data to the hospital electronic records from the participating NHS Trusts. This will enable determination of oncological outcome of the study cohort at 3 and 5 years follow up time points.

10.2 Informed consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. It is the responsibility of the 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 study. Consent can be taken during normal clinic appointments or on the day of surgery, if applicable. If the patient wishes to participate, written informed consent will be taken by the Principal Investigator, a trainee lead or an appropriately trained member of the team (as previously mentioned). Patients will be reminded that participation is voluntary and that they can withdraw at any time point without this affecting their care. This process will be clearly documented in the patients' medical notes. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained in the trial site file and a copy will be placed in the patient's notes. Consent will be sought specifically to determine oncological outcome of the study cohort with optional consent to donate archived tissue samples or slides for a future translational study. Patients will also be free to withdraw from the study at any time. Any data acquired prior to withdrawal will be included in the final analysis (unless consent is withdrawn by the participant). The reason for withdrawal will be recorded.

10.3 Study reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the REC, host organisation and Sponsor.

10.4 Patient confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

10.5 Archiving

In line with the principles of GCP/UK Clinical trial Regulations guidelines, at the end of the study, data will be securely archived at the centre for a minimum of 25 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately. No records may be destroyed without first obtaining written permission from the Sponsor.

10.6 Insurance

NHS indemnity through the Clinical Negligence Scheme for Trusts (CNST).

11. Public and Patient Involvement

MARECA study has been designed to collect and analyse information about tumour characteristics and treatment details for the patient's original and recurrent breast cancer. The study goal is to improve understanding of how this group of patients are currently being treated in the UK, as well as identify any variations in treatment. Following the patient's long term treatment outcome will enable the research team to study tumour characteristics and treatment details in order to identify patient groups where treatment outcome was suboptimal. This will in turn enable future research and treatments to be targeted and tailored in order to improve future patient outcome. Cancer recurrence and long term outcomes of treatment were key themes that emerged from the National Cancer Research Institute's 'living with and beyond cancer research priorities' project[69], who surveyed over 3500 patients, carers, and health and social care professionals.

We have gained valuable input from a patient representative group (Independent Cancer Patients' Voice, ICPV) in setting up the MARECA study, especially in drafting the patient information sheet and the patient consent form, which are concise and easy to understand from the patient and family member's point of view. We have ensured that these documents contain appropriate wording and phrases for patients eligible to join the study. This is especially important given the impact of cancer recurrence diagnosis to the patient and family members. We have also received positive feedback on the phrasing of the patient information sheet from the 'Pink Events', a breast cancer charity comprised of committee members who have been treated for breast cancer in the past.

12. Study Management

Oversight of the study will be by the Steering Group which is multidisciplinary and have wide regional representation. There will in addition be a smaller executive group for day to day management. It is expected that most of this work will be done as a 'virtual group' by email. A writing and data analysis group will also be convened. Oversight of the study will be by the MARECA Steering Group which will have wide representation from surgeons, oncologists, trainees, pathologists, research nurses, the professional societies, patient representatives and those with experience of study management and statistics.

13. List of participating units

The following UK breast units have agreed to participate in the study so far;

Hospital	Local PI
St. James's University Hospital, Leeds	Brian Hogan
The Royal Marsden Hospital, London	Peter Barry
University Hospital Southampton NHS Foundation Trust	Ramsey Cutress
Manchester University NHS Foundation Trust	Rajiv Dave
Bristol Breast Care Centre, North Bristol NHS Trust	Shelley Potter
University Hospitals of Leicester NHS Trust	Monika Kaushik
The Jasmine Breast Centre, Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust	Lynda Wyld
University College London Hospitals NHS Foundation Trust	Neill Patani
Oxford University Hospitals Foundation Trust	Dennis Remoundos
Belfast City Hospital	Stuart McIntosh
Bradford Royal Infirmary	Rick Linforth
Poole Hospital NHS Foundation Trust	Sarah Clark
Royal Victoria Infirmary, Newcastle	Henry Cain
Harrogate and District NHS Foundation Trust	Biswajit Ray
Castle Hill Hospital, Cottingham	Peter Kneeshaw

Glan Clwyd Hospital, Wales	Mandana Pennick
Addenbrooke's Hospital, Cambridge	John Benson
NHS Lanarkshire, Fife, and Forth Valley, Scotland	Chris Cartlidge
Royal Devon and Exeter NHS Foundation Trust	Charlotte Ives
The Mid Yorkshire Hospitals NHS Trust	Dan Glassman
Milton Keynes University Hospital	Gaural Patel
Royal Liverpool NHS Foundation Trust	Matthew Rowland
NHS Greater Glasgow and Clyde	Laszlo Romics
Calderdale and Huddersfield NHS Foundation Trust	Richard Frame
Chesterfield Royal Hospital NHS Foundation Trust	Julia Massey
Aberdeen Royal Infirmary	Beatrix Elsberger
Southend University Hospital NHS Foundation Trust	Harun Thomas
The Royal Wolverhampton NHS Trust	Raghavan Vidya
The Pennine Acute Hospitals NHS Trust	Kate Williams
East Sussex Healthcare NHS Trust	Ash Subramanian
Western Health and Social Care Trust, Northern Ireland	Brendan Skelly
University Hospital North Staffordshire, Stoke on Trent	Soni Soumian
University Hospital of Derby and Burton NHS Foundation Trust	Amit Goyal
Nottingham University Hospitals NHS Trust	Ellie Gutteridge
United Lincolnshire Hospitals NHS Trust	Dinesh Thekkinkattil
Royal United Hospitals Bath NHS Foundation Trust	Richard Sutton
Airedale NHS Foundation Trust	Elizabeth Baker
Maidstone and Tunbridge Wells NHS Trust	Karina Cox
North Tees and Hartlepool NHS Foundation Trust	Matei Dordea
Edinburgh Breast Unit, NHS Lothian	Matthew Barber
Bolton NHS Foundation Trust	Sreekumar Sundara Rajan
Gloucestershire Hospitals NHS Foundation Trust	Fiona Court
Sheffield Teaching Hospitals NHS Foundation Trust	Loaie Maraqa
Royal Surrey County Hospital NHS Foundation Trust	Liz Clayton
Royal Cornwall Hospitals NHS Trust	Polly King
York Teaching Hospital NHS Foundation Trust	Jenny Piper
Gateshead Health NHS Foundation Trust	Rob Milligan
University Hospitals Birmingham NHS Foundation Trust	Salena Bains
Hampshire Hospitals NHS Foundation Trust	Siobhan Laws
King's College Hospital NHS Foundation Trust, London	Sudeendra Doddi
Barts Health NHS Trust, London	Serena Ledwidge
Somerset NHS Foundation Trust	Zoe Goldthorpe
Countess of Chester Hospital NHS Foundation Trust	Anita Hargreaves
Norfolk and Norwich University Hospitals NHS Foundation Trust	Mina Youssef
West Hertfordshire Hospitals NHS Trust	Lee Min Lai
NHS Tayside	Alessio Vinci
Imperial College Healthcare NHS Trust	Daniel Leff
Southern Health & Social Care Trust	Helen Mathers
Royal Bournemouth Hospital	Anthony Skene
Hywel Dda University Health Board	Anita Huws

14. References

1. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero.
2. Independent, U.K.P.o.B.C.S., *The benefits and harms of breast cancer screening: an independent review.* Lancet, 2012. **380**(9855): p. 1778-86.
3. van Laar, C., et al., *Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients.* Eur J Cancer, 2013. **49**(15): p. 3093-101.
4. Holleczek, B., et al., *Risk of loco-regional recurrence and distant metastases of patients with invasive breast cancer up to ten years after diagnosis - results from a registry-based study from Germany.* BMC Cancer, 2019. **19**(1): p. 520.
5. https://www.nabcop.org.uk/content/uploads/2020/07/NABCOP-2020-Annual-Report-V1_high-res.pdf.
6. http://www.ncin.org.uk/view?rid=1043.
7. https://www2.tri-kobe.org/nccn/guideline/breast/english/breast.pdf.
8. Pinkney, T.D., et al., *Impact of wound edge protection devices on surgical site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial).* Bmj, 2013. **347**: p. f4305.
9. Ferguson, H.J., N.J. Hall, and A. Bhangu, *A multicentre cohort study assessing day of week effect and outcome from emergency appendicectomy.* BMJ Qual Saf, 2014. **23**(9): p. 732-40.
10. *Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy.* Br J Surg, 2013. **100**(9): p. 1240-52.
11. Lee, M.J., et al., *Current management of small bowel obstruction in the UK: results from the National Audit of Small Bowel Obstruction clinical practice survey.* Colorectal Dis, 2018. **20**(7): p. 623-630.
12. Pan, H., et al., *20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years.* N Engl J Med, 2017. **377**(19): p. 1836-1846.
13. Veronesi, U., et al., *Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer.* N Engl J Med, 2002. **347**(16): p. 1227-32.
14. Bosma, S.C., et al., *Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period.* Breast Cancer Res Treat, 2016. **156**(2): p. 391-400.
15. Zumsteg, Z.S., et al., *Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1-2N0 triple-negative breast cancer.* Ann Surg Oncol, 2013. **20**(11): p. 3469-76.
16. Taghian, A.G., et al., *Low locoregional recurrence rate among node-negative breast cancer patients with tumors 5 cm or larger treated by mastectomy, with or without adjuvant systemic therapy and without radiotherapy: results from five national surgical adjuvant breast and bowel project randomized clinical trials.* J Clin Oncol, 2006. **24**(24): p. 3927-32.
17. Houssami, N., et al., *The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis.* Ann Surg Oncol, 2014. **21**(3): p. 717-30.
18. Bodilsen, A., et al., *Importance of margin width in breast-conserving treatment of early breast cancer.* J Surg Oncol, 2016. **113**(6): p. 609-15.
19. Early Breast Cancer Trialists' Collaborative, G., et al., *Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of*

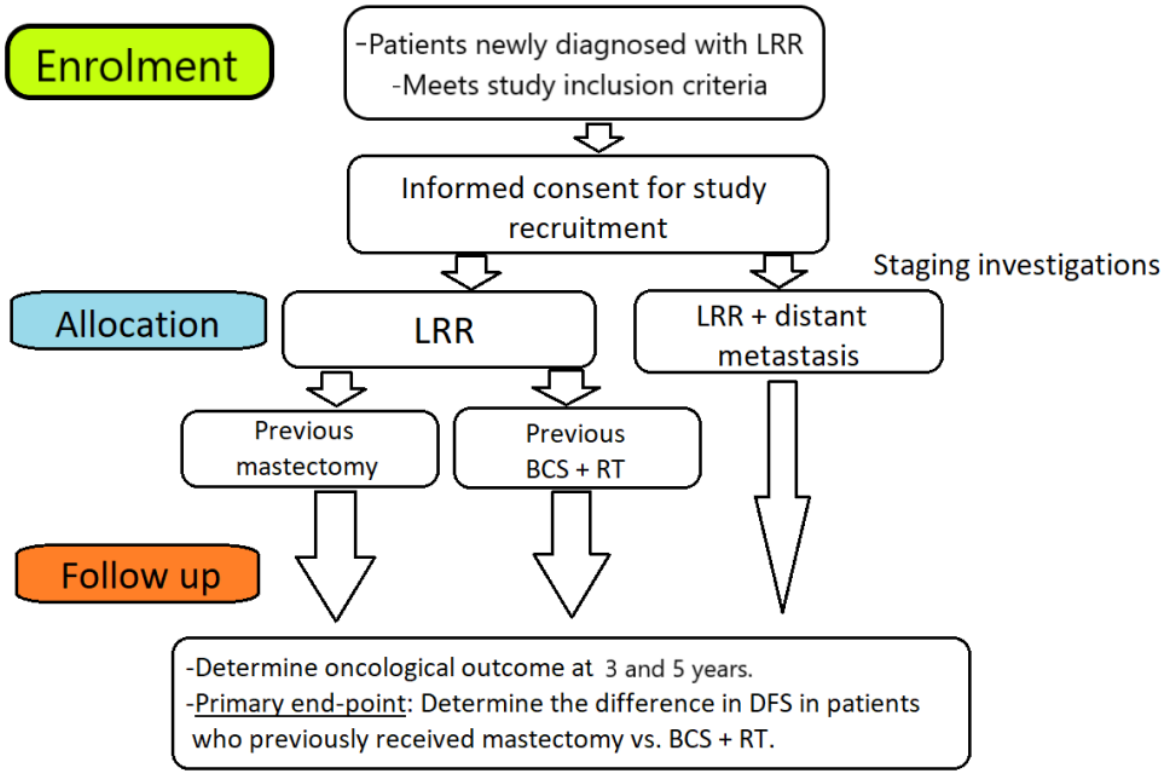
individual patient data for 10,801 women in 17 randomised trials. Lancet, 2011. **378**(9804): p. 1707-16.
20. Jones, H.A., et al., *Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial.* J Clin Oncol, 2009. **27**(30): p. 4939-47.
21. Coles, C.E., et al., *Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial.* Lancet, 2017. **390**(10099): p. 1048-1060.
22. Kunkler, I.H., et al., *Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial.* Lancet Oncol, 2015. **16**(3): p. 266-73.
23. Ebctcg, et al., *Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.* Lancet, 2014. **383**(9935): p. 2127-35.
24. Rezai, M., et al., *Translating the concept of intrinsic subtypes into an oncoplastic cohort of more than 1000 patients - predictors of recurrence and survival.* Breast, 2015. **24**(4): p. 384-90.
25. Bouganim, N., et al., *Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research.* Breast Cancer Res Treat, 2013. **139**(2): p. 603-6.
26. Arvold, N.D., et al., *Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy.* J Clin Oncol, 2011. **29**(29): p. 3885-91.
27. Kiess, A.P., et al., *Adjuvant trastuzumab reduces locoregional recurrence in women who receive breast-conservation therapy for lymph node-negative, human epidermal growth factor receptor 2-positive breast cancer.* Cancer, 2012. **118**(8): p. 1982-8.
28. Petrelli, F., et al., *Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials.* Breast Cancer Res Treat, 2013. **140**(2): p. 233-40.
29. Drukker, C.A., et al., *Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis.* Breast Cancer Res Treat, 2014. **148**(3): p. 599-613.
30. Carlson, J.J. and J.A. Roth, *The impact of the Oncotype Dx breast cancer assay in clinical practice: a systematic review and meta-analysis.* Breast Cancer Res Treat, 2013. **141**(1): p. 13-22.
31. McGuire, A., et al., *Locoregional Recurrence Following Breast Cancer Surgery in the Trastuzumab Era: A Systematic Review by Subtype.* Ann Surg Oncol, 2017. **24**(11): p. 3124-3132.
32. Radosa, J.C., et al., *Evaluation of Local and Distant Recurrence Patterns in Patients with Triple-Negative Breast Cancer According to Age.* Ann Surg Oncol, 2017. **24**(3): p. 698-704.
33. Rezai, M., et al., *Breast conservative surgery and local recurrence.* Breast, 2015. **24 Suppl 2**: p. S100-7.
34. Abi-Raad, R., et al., *Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy.* Int J Radiat Oncol Biol Phys, 2011. **81**(3): p. e151-7.
35. https://associationofbreastsurgery.org.uk/media/64765/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-2018-update.pdf.
36. Wapnir, I.L., et al., *Progress on BIG 1-02/IBCSG 27-02/NSABP B-37, a prospective randomized trial evaluating chemotherapy after local therapy for isolated locoregional recurrences of breast cancer.* Ann Surg Oncol, 2008. **15**(11): p. 3227-31.
37. Lee, M.Y., et al., *Clinicopathological Features and Prognostic Factors Affecting Survival Outcomes in Isolated Locoregional Recurrence of Breast Cancer: Single-Institutional Series.* PLoS One, 2016. **11**(9): p. e0163254.

38. van Tienhoven, G., et al., *Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group.* Eur J Cancer, 1999. **35**(1): p. 32-8.
39. Shenouda, M.N., et al., *Clinical outcome of isolated locoregional recurrence in patients with breast cancer according to their primary local treatment.* Clin Breast Cancer, 2014. **14**(3): p. 198-204.
40. Sirohi, B., A. Leary, and S.R. Johnston, *Ipsilateral breast tumor recurrence: is there any evidence for benefit of further systemic therapy?* Breast J, 2009. **15**(3): p. 268-78.
41. Wong, S.M. and M. Golshan, *Management of In-Breast Tumor Recurrence.* Ann Surg Oncol, 2018. **25**(10): p. 2846-2851.
42. Veronesi, U., et al., *Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events.* J Natl Cancer Inst, 1995. **87**(1): p. 19-27.
43. Yi, M., et al., *Classification of ipsilateral breast tumor recurrences after breast conservation therapy can predict patient prognosis and facilitate treatment planning.* Ann Surg, 2011. **253**(3): p. 572-9.
44. Kasumi, F., et al., *CIH-Tokyo experience with breast-conserving surgery without radiotherapy: 6.5 year follow-up results of 1462 patients.* Breast J, 2006. **12**(5 Suppl 2): p. S181-90.
45. Laird, J., et al., *Impact of an In Situ Component on Outcome After In-Breast Tumor Recurrence in Patients Treated with Breast-Conserving Therapy.* Ann Surg Oncol, 2018. **25**(1): p. 154-163.
46. Bollet, M.A., et al., *High-resolution mapping of DNA breakpoints to define true recurrences among ipsilateral breast cancers.* J Natl Cancer Inst, 2008. **100**(1): p. 48-58.
47. Vila, J., et al., *Conservative surgery for ipsilateral breast tumor recurrence.* J Surg Oncol, 2014. **110**(1): p. 62-7.
48. Al-Hilli, Z. and S.R. Grobmyer, *Management Strategies for Locally Recurrent Breast Cancer: Redo-Lumpectomy, Redo-Sentinel Node Biopsy, Redo-Radiation.* Ann Surg Oncol, 2019. **26**(10): p. 3018-3024.
49. Walstra, C., et al., *Repeat breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review.* Eur J Surg Oncol, 2019. **45**(8): p. 1317-1327.
50. Yoshida, A., et al., *Prognosis after mastectomy versus repeat lumpectomy in patients with ipsilateral breast cancer recurrence: A propensity score analysis.* Eur J Surg Oncol, 2016. **42**(4): p. 474-80.
51. Gentilini, O., et al., *Repeating conservative surgery after ipsilateral breast tumor reappearance: criteria for selecting the best candidates.* Ann Surg Oncol, 2012. **19**(12): p. 3771-6.
52. Poodt, I.G.M., et al., *Repeat Sentinel Lymph Node Biopsy for Ipsilateral Breast Tumor Recurrence: A Systematic Review of the Results and Impact on Prognosis.* Ann Surg Oncol, 2018. **25**(5): p. 1329-1339.
53. Poodt, I.G.M., et al., *Prognostic impact of repeat sentinel lymph node biopsy in patients with ipsilateral breast tumour recurrence.* Br J Surg, 2019. **106**(5): p. 574-585.
54. Fitzal, F., et al., *Impact of Breast Surgery in Primary Metastasized Breast Cancer: Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial.* Ann Surg, 2019. **269**(6): p. 1163-1169.
55. Badwe, R., et al., *Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial.* Lancet Oncol, 2015. **16**(13): p. 1380-8.
56. Soran, A., et al., *Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01.* Ann Surg Oncol, 2018. **25**(11): p. 3141-3149.

57. Wapnir, I.L., et al., *Efficacy of Chemotherapy for ER-Negative and ER-Positive Isolated Locoregional Recurrence of Breast Cancer: Final Analysis of the CALOR Trial.* J Clin Oncol, 2018. **36**(11): p. 1073-1079.
58. Forster, T., et al., *Second breast conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation.* J Contemp Brachytherapy, 2019. **11**(4): p. 312-319.
59. Clemons, M., et al., *Locoregionally recurrent breast cancer: incidence, risk factors and survival.* Cancer Treat Rev, 2001. **27**(2): p. 67-82.
60. Anderson, S.J., et al., *Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer.* J Clin Oncol, 2009. **27**(15): p. 2466-73.
61. Melvin, J.C., et al., *Progression of breast cancer following locoregional ipsilateral recurrence: importance of interval time.* Br J Cancer, 2016. **114**(1): p. 88-95.
62. Mylvaganam, S., et al., *Variation in the provision and practice of implant-based breast reconstruction in the UK: Results from the iBRA national practice questionnaire.* Breast, 2017. **35**: p. 182-190.
63. Obeid, J.S., et al., *Procurement of shared data instruments for Research Electronic Data Capture (REDCap).* Journal of Biomedical Informatics, 2013. **46**(2): p. 259-265.
64. Harris, P.A., et al., *Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of Biomedical Informatics, 2009. **42**(2): p. 377-381.
65. https://www.nice.org.uk/Guidance/CG164.
66. Vohra, R.S., et al., *Protocol for a multicentre, prospective, population-based cohort study of variation in practice of cholecystectomy and surgical outcomes (The CholeS study).* BMJ Open, 2015. **5**(1).
67. Harms, W., et al., *Current Treatment of Isolated Locoregional Breast Cancer Recurrences.* Breast Care (Basel), 2015. **10**(4): p. 265-71.
68. Aebi, S., et al., *Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial.* Lancet Oncol, 2014. **15**(2): p. 156-63.
69. https://www.ncri.org.uk/lwbc/.

15. Appendix

MARECA study flowchart



MARECA study National Practice Questionnaire on management of breast cancer locoregional recurrence

Management of breast cancer patients who present with locoregional recurrence was highlighted as a key research priority at the Association of Breast Surgery Gap Analysis meeting in 2019. Breast cancer locoregional recurrence is defined as breast cancer recurrence (invasive or DCIS) within the conserved breast, the ipsilateral skin or chest wall following mastectomy, or in the ipsilateral regional lymph nodes (axilla, supra- or infra-clavicular, or internal mammary nodes). Currently there is no UK specific guideline on how these patients should be managed.

This questionnaire will aim to evaluate how UK breast units are managing patients with LRR. This will be followed by the MARECA study- National Study of Management of Breast Cancer Locoregional Recurrence and Oncological Outcome. This is a prospective observational multicentre cohort study which will describe the current management and prognosis of patients diagnosed with breast cancer locoregional recurrence in the UK.

We would like you to answer the National Practice Questionnaire within your entire MDT

team (maybe before or after the MDT meeting when all team members are present). The questionnaire will take approximately 20 minutes to complete and consists of questions about the number of cases your unit deals with followed by some scenario based questions designed to capture data on practice variation and areas of uncertainty.

Basic Unit information

-Please state the name of the participating hospital

-Please state the name, email address, and job title of the person entering data for your unit's questionnaire

-Does your unit treat patients referred from the breast screening programme?

Yes/No

-How many new breast cancers (invasive cancer and DCIS) do you manage per calendar year?

-Does your unit keep a prospective database of patients diagnosed with breast cancer LRR?

Yes/No

-Does your trust submit data on breast cancer recurrence to a national database?

Yes/No (If Yes, what data collection system is used? e.g. COSD)

-As an estimate, how many patients with LRR (without distant metastasis) do you manage at your unit per year?

- Less than 5 patients per year
- 5 to 10 patients per year
- More than 10 patients per year

-As an estimate, how many patients with LRR (with distant metastasis) do you manage at your unit per year?

- Less than 5 patients per year
- 5 to 10 patients per year

- More than 10 patients per year

Practice Questionnaire Scenarios

MDT attendance for the National Practice Questionnaire

-Please state the presence and number of participating MDT members;

- Consultant Breast Surgeon (Yes/No; state number present)
- Consultant Oncologist (Yes/No; state number present)
- Consultant Histopathologist (Yes/No; state number present)
- Consultant Radiologist (Yes/No; state number present)
- Breast surgery trainees (Yes/No; state number present)
- Oncology trainees (Yes/No: state number present)
- Breast Care Nurses (Yes/No; state number present)
- Other MDT members (please state role and state number present)

Scenario 1. Diagnosis and staging investigations

-A 50 years old patient presents with a 3cm invasive recurrence in the ipsilateral breast after previous breast conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) 3 years ago. The recurrence is in the same quadrant and has the same molecular receptor status as the original cancer. The tumour does not involve the skin or chest wall. Does your unit perform an axillary ultrasound scan (USS)?

Always/Usually/Occasionally/Never

-If this patient had previous axillary node clearance (ANC) instead of SLNB, does your unit perform an axillary USS?

Always/Usually/Occasionally/Never

-Would your unit offer staging investigations for this patient?

Always/Usually/Occasionally/Never

If yes, which staging investigations would be recommended (please tick all that apply)?

- CT chest/abdomen/pelvis
- Blood tests (e.g. FBC, U+E, LFTs, Ca, CA15-3)
- Isotope bone scan
- PET CT
- Others (please specify)

-If this patient had instead presented with an invasive recurrence in a different breast quadrant with a different molecular receptor status as the original cancer, would your unit offer staging investigations?

Always/Usually/Occasionally/Never

If this patient was found to have concurrent distant metastasis, would your MDT offer resection of the in-breast recurrence?

Always/Usually/Occasionally/Never

Scenario 2. Surgery to the breast

-A 76 year old patient underwent BCS and SLNB 10 years ago, followed by whole breast radiotherapy (WBRT). The previous histology had shown a 10mm area of grade 2 invasive ductal carcinoma (IDC) which was ER strongly positive and Her-2 negative. She had 3 nodes removed at SLNB of which none were positive. She had 5 years of letrozole treatment after surgery.

She now presents with a 1cm recurrent grade 1 ER+HER2- IDC 3 cm away from the primary scar. She wears a DD cup bra size and has good symmetry. She is fit and well. Would your MDT offer repeat BCS for this patient?

Always/Usually/Occasionally/Never

-If this patient had not received previous WBRT (she was PRIME 2 compliant), would your MDT offer repeat BCS?

Always/Usually/Occasionally/Never

-If your MDT offers repeat BCS for patients who had previously been treated with BCS and radiotherapy, does your MDT offer repeat breast radiotherapy?

Always/Usually/Occasionally/Never

Scenario 3. Axillary Management

-A 40 year old patient underwent BCS and SLNB for a 2.5cm grade 3 ductal cancer 3 years ago in the upper outer quadrant. Disease was resected with a clear margin and none of 2 lymph nodes contained any cancer. The disease was ER+ and Her2 negative. She had post-operative WBRT plus boost, chemotherapy, and 5 years of tamoxifen.

She now presents with an in-breast invasive local recurrence close to the primary scar measuring 10mm. Her pre-operative axillary assessment is benign clinically and on ultrasound. Staging is clear. What is your MDT's preferred mode of axillary management?

- Axillary Node Sampling (ANS: 4 node sample)
- Axillary Node Clearance (ANC)
- No axillary surgery
- Repeat SLNB without lymphoscintigram
- Repeat SLNB plus pre-operative lymphoscintigraphy
- Other (please specify)

-If this patient undergoes repeat SLNB and no SLN can be identified using your unit's standard tracer technique, how do you proceed?

- No further axillary dissection
- ANS
- ANC
- Other (please specify)

Scenario 4. Adjuvant treatment and patient follow up

-A fit and well 65 year old patient was treated with mastectomy and SLNB for a grade 3 node negative ER+HER2- 3cm IDC 7 years ago. She received adjuvant chemotherapy (3 cycles of anthracycline + cyclophosphamide, then 3 cycles of taxane) due to high Oncotype Dx score and completed 5 years of endocrine therapy. She did not require post mastectomy radiotherapy.

She now presents with a 1.5cm mastectomy skin flap invasive recurrence which is mobile. Staging is clear and she undergoes wide local excision of the skin flap and axillary surgery. Her resection margins are clear with negative lymph nodes. If this recurrent cancer was a grade 2 ER+HER2- IDC, would your MDT recommend adjuvant chemotherapy for this patient?

Always/Usually/Occasionally/Never

-If your unit offers Ki-67 testing, does your unit perform Ki-67 testing on the recurrent cancer in order to inform adjuvant chemotherapy decision-making for this patient?

Always/Usually/Occasionally/Never (Ki-67 test only utilised for primary breast cancer)/Not applicable as Ki-67 test not routinely offered at the unit

-Would your MDT recommend radiotherapy to the chest wall for this patient?

Always/Usually/Occasionally/Never

-For this scenario, if the patient had instead developed the ER+HER2- local recurrence 3 years after her primary breast cancer surgery (i.e. whilst still on adjuvant endocrine therapy), what adjuvant treatment(s) would your MDT recommend?

- Continue with current endocrine therapy + consider chemotherapy
- Continue with current endocrine therapy + no chemotherapy
- Switch endocrine therapy + consider chemotherapy
- Switch endocrine therapy + no chemotherapy
- No further endocrine therapy + consider chemotherapy
- No further endocrine therapy + no chemotherapy
- Other (please specify)

-For this scenario, if at the time of the recurrent cancer (ER+HER2- IDC) resection, she was instead found to have 1/3 macrometastasis in her axillary lymph node, would your MDT recommend adjuvant chemotherapy for this patient?

Always/Usually/Occasionally/Never

-For this scenario, if the patient had instead developed a recurrent cancer which was grade 3 triple negative IDC (and node negative), would your MDT recommend adjuvant chemotherapy for this patient?

Always/Usually/Occasionally/Never

Patient follow up policy

-Are patients in your unit followed up in the clinic after treatment for breast cancer LRR?

- No routine follow up
- Surgical clinic
- Oncology clinic

- Both surgical and oncology clinic follow up
- Other (please specify)

-What is the total duration of clinic follow up for these patients?

- 1 year
- 2 years
- 3 years
- 4 years
- 5 years
- No follow up protocol with individualised follow up
- Other (please specify)

Thank you very much for taking time to complete the survey. We are in the process of setting up a national study of **ma**nagement of breast cancer locoregional **re**currence and oncologi**cal** outcome (the MARECA study). We welcome participation from all UK breast units. Please email the study team (leedsth-tr.themarecastudy@nhs.net) to register your interest. We especially welcome participation from trainees.

MARECA study Gantt chart