ANZ1002: Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial (PROSPECT)

A single arm phase II study using magnetic resonance imaging (MRI) to select patients with early breast cancer for omission of post-operative radiotherapy

PROTOCOL NUMBER	ANZ1002
SPONSOR	Breast Cancer Trials
ANZCTRN	12610000810011
Protocol Version	Amendment 7, 4th April 2022

Protocol Version History:

Date	Type	Number
September 2010	Original	Version 1.0
November 2010	Amendment	1
January 2013	Amendment	2
December 2013	Amendment	3
October 2017	Amendment	4
12th November 2020	Amendment	5
18th October 2021	Amendment	6
4th April 2022	Amendment	7

ANZ1002 (PROSPECT) Steering Committee

Study Chair

Scientific Advisory Committee Chair

Director of Research or designee

Trials Department representatives (COO-Research/Project Leader)

Trial Statistician

Trial Pathologist

Principal Investigators from participating institutions

Consumer Advisory Panel representative

Trial Personnel

Study Chair: Professor Bruce Mann

[redacted]

Trial Statistician: Professor Val Gebski

[redacted]

Trial Coordination and Registration: Breast Cancer Trials

[redacted]

PROTOCOL SIGNATURE PAGE

ANZ1002 (PROSPECT)

Amendment 7, 4th April 2022

Approved by:

Director of Research, Breast Cancer Trials

Professor GB Mann

Signature on file at BCT Date: _____

Approved by:

Trial Statistician, Breast Cancer Trials

Professor V Gebski

Signature on file at BCT Date: _____

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

ANZ1002 (PROSPECT)

Amendment 7, 4th April 2022

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol, all applicable regulations and guidelines, the Declaration of Helsinki and ICH Good Clinical Practice (GCP).

Name of Principal Investigator: _____

Signature: _____ Date: _____

SYNOPSIS

Full trial title

A single arm phase II study using magnetic resonance imaging (MRI) to select patients with early breast cancer for omission of post-operative radiotherapy.

Patient population

Women aged ≥50 with histologically diagnosed unilateral, unifocal invasive primary breast cancer, T1, pN0, M0, any grade, radial margins must be ≥2 mm clear of invasive cancer and any DCIS; good performance status (0-1) and no contraindications for MRI.

Not eligible:

- Patients with triple negative (ER negative, PR negative, HER2 not amplified) disease

(Refer to Section 3 Eligibility Criteria)

Rationale

Breast cancer is the most common serious malignancy in Australian women and most are suitable for breast conserving therapy. Subsequently, thousands of women with early invasive breast cancer undergo adjuvant breast radiotherapy each year. Patients bear the costs, inconvenience and morbidity of radiotherapy as for most patient's, breast conserving surgery without adjuvant radiotherapy may not be safe [1, 2]. Prior attempts to identify large subsets of patients for whom radiotherapy can be safely omitted have failed, and so radiotherapy is currently only occasionally omitted in women over 70 with small low risk cancers[3]. Identification of a much larger subset of patients in whom adjuvant radiotherapy could be safely omitted would be hugely significant, not only to the patients, but to the entire health system.

The innovative aspect of this study is that it will use a new technology – breast MRI – in a novel way, to address a long-standing clinical problem. While MRI has shown merit in recent retrospective studies in the setting of partial breast irradiation[4-6], this prospective study is more rigorous and takes the next logical step, which is to use MRI adjunctively to select a subset of breast cancer patients in whom radiotherapy could be safely avoided altogether.

If this study demonstrates an acceptably low rate of local recurrence, a multicentre Phase III randomised controlled trial investigating the use of MRI to select patients in whom RT can be omitted will be proposed and a health economic assessment will be planned. If it is found radiotherapy can be omitted without compromising local recurrence, it could significantly alter the management of women with early breast cancer as well as decrease costs to the health care system. There are benefits of safely foregoing radiotherapy in low risk women which are particularly significant for rural and remote women, who frequently choose total mastectomy to avoid the need to have a treatment that requires them to be absent from home for a prolonged period. If this study is successful, the extra cost of a small number of MRI scans will far outweigh the

cost of 5 weeks of radiotherapy and the costs of potential side effects of radiotherapy for each patient found not to need radiation.

Objective

To determine the ipsilateral invasive recurrence rate (IIRR) in patients with favourable clinico-pathological features on MRI and unequivocally unifocal breast cancer treated with wide local excision but no adjuvant radiotherapy.

Trial end points

Primary

- Ipsilateral invasive recurrence rate in the breast at 5 years

Secondary

- Ipsilateral invasive recurrence rate in the breast at 10 years
- Ipsilateral DCIS recurrence rate in the breast at 5 and 10 years
- Regional recurrence rate at 5 and 10 years
- Distant recurrence rate at 5 and 10 years
- Contralateral breast cancer rate at 5 and 10 years
- Breast-cancer specific survival rate at 5 and 10 years
- Overall survival rate at 5 and 10 years

Statistical analysis

This is a single arm phase II study investigating the impact of omission of radiotherapy in low risk patients with early breast cancer with MRI performed at 18 months to detect potential early local recurrence. Based on the assumption that omission of radiotherapy would be acceptable if the ipsilateral invasive recurrence rate (IIRR) was 5% at 5 years; a IIRR of >7% would not be acceptable. It is expected that 30-35 HER2 positive patients and 165-170 HER2 negative patients will be recruited.

Other descriptive analyses

The entire cohort of patients undergoing pre-operative staging MRI will be included in descriptive analyses of:

- A substudy of the outcome of MRI at breast cancer diagnosis, the impact of MRI and the accuracy of MRI (Appendix H).
- An economic evaluation to determine the potential cost-effectiveness of implementing a protocol where women with cT1cN0 hormone receptor-positive and/or HER2 positive early stage breast cancer undergo a pre-surgical MRI (and for those women where the MRI clearly shows no synchronous cancer lesions radiotherapy is omitted) compared to standard practice (no MRI and all women receive radiotherapy (Appendix I).

- A substudy of outcomes for pre-registered patients who underwent MRI but were deemed unsuitable for inclusion in the main study, who consent to follow-up, to understand the full impact of MRI before initial surgery (Appendix J).
- A substudy (Appendix K) to:
  - Conduct sequencing of the index and subsequent lesions to determine whether they are true recurrences or whether they are independent lesions
  - Analysis of the index lesion where there has been a subsequent event using the PAM50 assay, to determine whether it may identify those at high risk of recurrence.

Sample size and anticipated trial duration

200 patients are expected to be recruited, with follow up for up to 10 years, or until the final analysis.

Procedures

Pre-registration – pre-operative MRI scan (≤ 6 weeks prior to first excisional surgery)

Registration – determine eligibility and register within 8 weeks of final excisional surgery

Post-registration - all patients:

- Clinical review every 3 months for the first 6 months post final excisional surgery followed by,
- 6 monthly review for 5 years
- 12 monthly review until 10 years or until the final analysis, whichever occurs first
- A mammogram will be performed 6 months post final excisional surgery and annually thereafter
- A MRI will be performed 18 months post final excisional surgery.

Figure 1 Study Schema

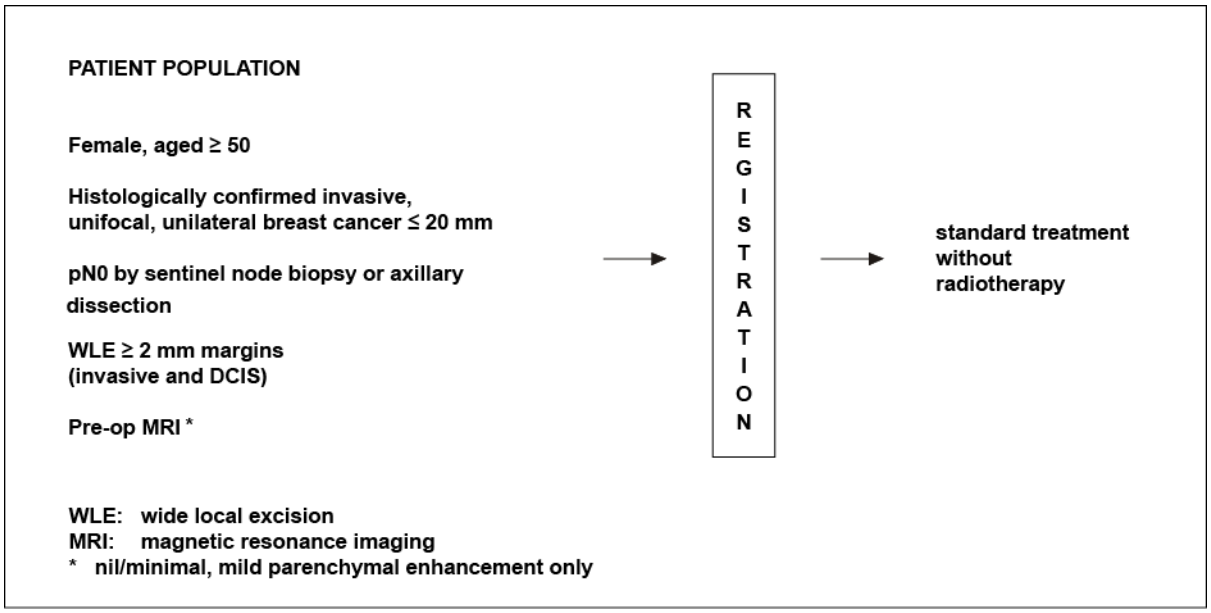


Table of Contents

Table of Tables

Table of Figures

Appendices

Table 1 List of Abbreviations

AD	Axillary Dissection
AE	Adverse Event
BC	Breast Cancer
BCT	Breast Conserving Therapy
BRCA	BReast CAncer gene
CRF	Case Record Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eGFR	Estimated Glomerular Filtration Rate
EIC	Extensive Intraductal Component
ER	Oestrogen Receptor
HER2	Human Epidermal Growth Factor Receptor 2
IHC	Immunohistochemistry
LN	Lymph Node
LR	Local Recurrence
IIRR	Ipsilateral Invasive Recurrence Rate
LVI	Lymphovascular invasion
MMG	Mammogram
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
PBI	Partial Breast Irradiation
pN0	No regional lymph node metastasis histologically
R0	Clear surgical margins
RT	Radiotherapy
SAE	Serious Adverse Event
SN	Sentinel Node
WLE	Wide Local Excision

1 INTRODUCTION

1.1 Background/Rationale

1.1.1 Standard practice

Since trials in the 1970s in early breast cancer showed no difference in survival between total mastectomy and breast conserving therapy (BCT) which included whole breast radiotherapy (RT) after wide local excision, the latter has become standard practice for most early breast cancer [7-10].

1.1.2 Role of radiotherapy, local recurrence and risks of radiotherapy

Radiotherapy is used to decrease local recurrence (LR). The randomised trials of BCT reported local recurrence rates (LRR) of 3-18%[7, 10-12]. These trials included varying tumour sizes and were not confined to patients with low risk. An Oxford overview of the role of RT analysed 23,500 patients including 7,300 patients who had breast-conserving surgery. An overall risk reduction in LR at 5 years from 26% to 7% and an absolute 5% reduction in overall mortality were reported[1, 2]. Lymph Node (LN)-positivity was a major risk for LR and in the LN-negative group, young age, poor differentiation and large size were associated with increased LR.

Radiotherapy for BCT is generally well tolerated. However, it is inconvenient (a standard course involves 25 visits over 5 weeks), has short term side-effects, may have long term side effects including discomfort in the breast and altered skin sensation, a small risk of radiation pneumonitis and cardiac effects and a very low incidence of radiation-induced sarcoma[13-16]. In light of the high incidence of breast cancer, it is also a major consumer of resources in our health system.

Defining a group in which RT can be omitted after breast conserving surgery is a long-standing focus of clinical investigators[17-19]. Six more recent trials have attempted to identify a group where the benefits of RT may be insignificant. The CALGB trial C9343 included women over 70 years old, with oestrogen receptor positive (ER+ve) tumours <2 cm, who were clinically LN-negative and received hormone therapy. At 7.9 years median follow up the LRR with and without RT was 1% vs 6.3% respectively with identical breast-cancer specific mortality (2%) and overall all-causes mortality of 26%[20]. The authors concluded that, given that no difference in regional or distal metastases was demonstrated, RT could be reasonably omitted in these low risk women[3]. Fyles et al. randomised 769 patients >50 yrs, with ≤ T2 tumours to tamoxifen and RT versus tamoxifen alone. A 6% benefit was seen with RT with 4.6% benefit in local recurrence in the T1 subset (3.2% versus 7.8%)[21]. Tumour size >2 cm, ER negativity, and higher pathological grade were associated with LR. An exploratory subgroup analysis concluded that T1 tumours in patients who were >60 years and who were ER positive may be a low risk group [21].

Some larger trials such as NSABP B21 revealed a benefit of radiotherapy of 11% decrease in LRR with RT[22] although other smaller trials supporting radiotherapy have not considered adjuvant endocrine treatment [23]. Another recent study of 749 patients 55-

75 years old, with tumours <2.5 cm and <3 LN positive were included regardless of receptor status (88% ER positive). Systemic treatment was given according to nodal status and biological need, mirroring current standard treatment. At a minimum of 53 months follow up, the LRR was 2.5% vs 0.7% in surgery alone and RT arms respectively, with no difference in distant disease free survival or overall survival[24].

The results of ongoing prospective trials such as the BASOII trial[25, 26] and the PRIME II study including women with early breast cancer and adjuvant endocrine treatment[27] may further elucidate the role of radiotherapy in modern breast cancer management.

A recent consensus recommendation from an International Expert Panel support the routine use of RT except possibly in low risk T1 older patients[28].

1.1.3 What factors are associated with higher risk of local recurrence?

Trials have been variable in identifying factors associated with an increased risk of local recurrence[7]. In general the following factors have been implicated: Inadequate surgical margin (<1 mm); Extensive DCIS in and around the cancer; Lymphovascular invasion (LVI); Grade III; LN positivity; Tumour size >20 mm; Age <50; ER negativity; Multifocality; BRCA 1, 2 mutation carriage[29-32].

Recent studies suggest that "Triple Negative" cancers have a higher LR risk after wide excision and RT. HER2 positivity was associated with increased LR across all tumour sizes in series prior to widespread use of adjuvant trastuzumab [33, 34].

1.1.4 Magnetic resonance imaging in the breast

Magnetic resonance imaging (MRI) of the breast sometimes identifies breast pathology that is occult to mammography and ultrasound examination. Currently breast MRI is only funded for surveillance of high risk patients under the age of 50 years. Due to reports of MRI detection of additional foci of synchronous disease in the ipsi- or contralateral[35] breast at the time of diagnosis, it has been included in the algorithm of management of early breast cancer in some international centres and Australian practices, but without clinical trial evidence to support its use.

The presence of additional foci has been well-established by anatomical studies involving serial sectioning of mastectomy specimens and range from 21-63%[36-41]. Additional foci are often near (2-4 cm) the index cancer. Despite this multifocality and multicentricity, adjuvant whole breast-radiation has provided equivalent survival to mastectomy[7]. More recently, MRI findings have been directly compared to serial sectioning for DCIS and invasive cancer. Sardanelli et al[42] performed serial sections in 90 patients who had pre-operative MRI and mammographic imaging. The sensitivity of MRI for invasive cancer was 89% (66% for mammogram p<0.001) but only 40% for DCIS (no significant difference with mammography). There were 19 false negative cases and 30 false positive cases; the positive predictive value was 68% for MRI. MRI was particularly of use in the dense breast. Kuhl et al.[43] evaluated pure DCIS showing much higher sensitivity for detection of DCIS of 98% (compared to mammogram 56%, p<0.0001). The variation in MRI sensitivity for both DCIS and invasive disease is striking but these studies form the best comparators of MRI and histology.

The accuracy and impact of MRI on treatment was summarised in a 2008 meta-analysis by Housaami et al[44]. Nineteen studies involving 2610 women were included where the MRI-only detection of foci was documented. Additional foci, either multifocal or multicentric were identified in 16% (range 6-34%); 66% were histologically confirmed as malignant. For those who had additional biopsy-proven additional foci, conversion from wide local excision (WLE) to mastectomy occurred in 8.1% and conversion from WLE to wider or additional excision occurred in 11.3%. In those who did not have histologically-proven additional foci (false positives), the conversion from WLE to mastectomy was 1.1% and from WLE to wider or additional excision was 5.5%. In summary, of every three women with additional lesions detected by MRI only, two will have an additional cancer (true positive) and one will have a false positive. This meta-analysis highlighted that whilst MRI detected additional foci resulting in more extensive surgery, the clinical impact was not clear[44, 45].

Tumour extent and multifocality is important in invasive lobular carcinoma. The diffuse growth pattern of classical lobular carcinoma may make tumour extent difficult to assess with mammography especially in dense breasts. MRI has frequently been reported to be of use in lobular carcinoma due to this multifocality[46]. The sensitivity of MRI in lobular cancer is reported as 93.3% in a meta-analysis published by Mann et al, which included 209 patients[47]. While lobular cancers mainly present as irregular spiculated masses, non-mass-like enhancement is more common than with invasive ductal carcinoma. In correlation studies of MRI and pathology in lobular carcinoma[48-50], the accuracy of detection of multifocality is between 80-90% but overestimation and underestimation remains an issue. The heterogeneity between studies was an issue in the meta-analysis, but more recently Mann has published an estimate of the correlation coefficient between pathology and MRI for lobular carcinoma of 0.89 (compared to an estimate of 0.22 for mammography and ultrasound)[51]. Additional disease was detected in 32% of patients.

The discovery of additional foci might lead to more extensive surgery with potentially improved local recurrence rates. The UK COMICE study is the only prospective, randomised controlled trial to examine pre-operative breast MRI in early stage breast cancer from 45 centres involving 1623 women[52]. Re-excision rates were the primary objective. Patients with biopsy-proved breast cancer were randomised to MRI or no further imaging. Re-excision rates were 19% irrespective of MRI use (p=0.77). The overall mastectomy rate was 13% in the MRI group and 8.8% in no MRI group (p=ns).

The clinical benefit of MRI in early breast cancer staging was assessed in a retrospective study by Solin et al [53]. in 756 patients with early breast cancer. Of the MRI scans, 50% were performed prior to the first excisions. Patients who went on to mastectomy as a result of MRI were excluded from analysis. The local failure rate was only 3-4% across this group, and not significantly different between those who had pre-operative MRI and those who did not. A selection bias for young women possibly due to increased breast density on mammography was evident. However, the conclusion was that in the

setting of post-operative radiotherapy, MRI is not globally indicated in the staging of patients undergoing BCT.

Fischer et al retrospectively analysed 121 patients with pre-operative MRI compared to 225 without MRI and showed a 1.2 % LRR in those with MRI v 6.5% LR in those without ($p<0.001$), concluding that pre-operative MRI appropriately affected surgical management [54]. The group have subsequently shown a benefit of MRI with MR-guided biopsy to confirm additional disease especially in mammographically dense breasts and lobular carcinoma[55]. However, Hwang et al.[56] showed no difference in ipsilateral breast tumour recurrence in a retrospective study with a rate of 1.6% and 2.6% with MRI use or no MRI use respectively (follow up range 19-26 months).

MRI is unlikely to significantly reduce the LRR in BCT for early breast cancer with standard adjuvant treatment as the LRR is already very low in this group (0.07-4% at 5 years) [3, 10, 21, 22]. The prospect of using MRI to tailor the approach to breast radiotherapy has been evaluated in the setting of partial breast irradiation (PBI)[4-6]. These studies have been retrospective with various entry criteria. The rate of occult synchronous breast cancer varied between 5-10%.

Al-Hallaq et al[6] performed a retrospective analysis of 450 patients of whom 110 were eligible for PBI. Additional disease (multifocal or multicentric) was found in 10% with a false positive rate of 4.5%, supporting MRI prior to consideration of PBI. Similarly, Godinez et al detected proven additional disease in 38%; 10% of these cases were identified in a different quadrant to the index cancer [4]. Tendulkar et al reported additional disease with MRI in 5.8% of cases being considered for PBI[5].

This trial takes these considerations further, and tests the hypothesis that patients with an unequivocally unifocal breast cancer on MRI and favourable clinical and pathological features can safely be treated with wide excision alone.

1.1.5 Other descriptive analyses

The entire cohort of patients undergoing pre-operative staging MRI will be included in descriptive analyses of:

- A substudy of the outcome of MRI at breast cancer diagnosis, the impact of MRI and the accuracy of MRI (Appendix H).
- An economic evaluation to determine the potential cost-effectiveness of implementing a protocol where women with cT1cN0 hormone receptor-positive and/or HER2 positive early stage breast cancer undergo a pre-surgical MRI (and for those women where the MRI clearly shows no synchronous cancer lesions radiotherapy is omitted) compared to standard practice (no MRI and all women receive radiotherapy (Appendix I).
- A substudy of outcomes for pre-registered patients who underwent MRI but were deemed unsuitable for inclusion in the main study, who consent to follow-up, to understand the full impact of MRI before initial surgery (Appendix J).

- A substudy (Appendix K) to:
  - Conduct sequencing of the index and subsequent lesions to determine whether they are true recurrences or whether they are independent lesions
  - Analysis of the index lesion where there has been a subsequent event using the PAM50 assay, to determine whether it may identify those at high risk of recurrence.

2 PRIMARY OBJECTIVE

To determine the ipsilateral invasive recurrence rate (IIRR) in patients with favourable clinico-pathological features on MRI and unequivocally unifocal breast cancer treated with wide local excision but no adjuvant radiotherapy.

3 ELIGIBILITY

3.1 Inclusion Criteria

For inclusion in the trial, patients must fulfil all of the following criteria:

1. Female patients ≥50 years old with histologically confirmed, unifocal*, unilateral invasive breast cancer
2. In good health and suitable for prolonged follow up with a life expectancy of at least 5 years
3. Breast conserving surgery with invasive primary tumour (including any surrounding DCIS) ≤20 mm
4. Resection margins must be ≥2 mm clear of any invasive cancer and ≥2 mm clear of any DCIS. However, superficial or deep margins of <2 mm for invasive cancer and DCIS are allowed if all breast tissue from the subcutaneous tissue or pectoralis fascia respectively was removed and radial margins are ≥2 mm for invasive cancer and DCIS
5. pN0 by sentinel node biopsy and/or axillary dissection
6. Mammogram must have been performed within 3 months prior to first excisional surgery for breast cancer and must show unifocal* breast cancer
7. Pre-operative MRI must be performed after the patient and the investigator sign screening consent and no more than 6 weeks prior to the first excisional surgery for breast cancer
8. Radiological imaging (Ultrasound, Mammogram and MRI) must be made available for central review as part of the quality control measures for this trial. In the event of an interpretation discrepancy between the local site and the central review, the central review interpretation will be used to determine eligibility. Refer to section 6.1.2
9. Parenchymal enhancement on pre-operative MRI must be defined as nil/minimal or mild. In the event of an interpretation discrepancy between the local site and the central review, the central review interpretation will be used to determine eligibility
10. Pathology material from any ipsilateral recurrence (invasive tumour and/or DCIS) must be available for submission for central review as part of the quality control measures for this trial. Refer to section 9.1.2
11. ECOG performance status 0-1
12. Written informed consent must be signed and dated by the patient and the investigator prior to registration to the trial
13. Patients must be informed of and agree to data and tissue material transfer and handling, in accordance with national data protection guidelines

14. Patients must be registered within 8 weeks after final breast surgery and be accessible for long term follow up
15. Patients must cease all hormonal contraceptives and hormone replacement therapies within 4 weeks following histological diagnosis of invasive breast cancer
16. Patients must agree to comply with systemic treatment recommendations (e.g. hormonal therapy for ER+/PR+ tumours, trastuzumab for HER2 positive cancers)

* Where histopathology is unable to identify a 'bridge' of tumour tissue joining two or more apparent invasive cancer foci the following will be used to confirm unifocal disease:
  - All foci must be of the same histology
  - All foci must have the same hormone (ER and PR) and HER2 neu status
  - In relation to criteria 3.1.2: the overall tumour size (including additional foci of DCIS) must remain ≤20 mm. The tumour size is defined as the longest distance between the outer most edges of all foci, the space between the two or more foci is included in the overall size: Size = ('Foci A + Foci B + 'the distance between A and B').

3.2 Exclusion Criteria

A patient who has any of the following criteria will be excluded from the study:

1. Diagnostic MMG shows prominent calcification in the index lesion.
2. Triple negative cancers (ER-ve and PR-ve and HER2-ve) where ER and PR positivity is defined as ≥1% staining on IHC(57)
3. Previous in-situ or invasive breast cancer
4. Patients who have had a mastectomy
5. Extensive DCIS (Extensive Intraductal Component (EIC)). Extensive DCIS is defined as invasive carcinoma with the following three components:
   a. DCIS is present within the invasive tumour; and
   b. DCIS within invasive tumour comprises more than 25% of the invasive tumour volume; and
   c. DCIS exists beyond the margin of the invasive tumour
6. Lymphovascular invasion; Multifocal/multicentric breast cancer; Distant metastasis at diagnosis or bilateral breast cancer
7. HER2 positive patients who will not receive trastuzumab as part of adjuvant systemic therapy
8. Gene carriers (BRCA 1,2) or those whose family history of breast cancer reaches the high-risk category of the Cancer Australia (refer to Appendix E)

9. Contraindication to MRI scanning (estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2, pacemaker, implanted non MRI compatible devices, cochlear implants, neurostimulators, insulin infusion pumps, pregnancy or lactation)
10. Moderate or marked background parenchymal enhancement on pre-operative MRI. In the event of an interpretation discrepancy between the local site and the central review, the central review interpretation will be used to determine eligibility.
11. Concurrent illness/conditions which limits life expectancy to 5 years.

3.3 Substudies of Pre-registered Patients (Appendices I & J)

Patients who have had MRI and subsequently been deemed ineligible for the main study will be asked to consent for further research on descriptive analyses.

4 RECRUITMENT

A secure web-based screening log has been developed to keep a record of screened potential participants. The screening log will be made available to study nurses/data managers at participating institutions; these staff can only access the screening log specific to their own institution.

The BCT website (www.breastcancertrials.org.au) public access area contains a section dedicated to the ANZ 1002: PROSPECT trial where women can obtain information about the trial.

BCT will actively promote the trial throughout Australia and New Zealand through newsletters and cancer consumer networks (e.g. the Breast Cancer Network Australia). BCT may promote this trial to the general public by generating media releases, community service announcements, advertising and producing YouTube videos. Staff at participating institutions will also be encouraged to promote the trial locally.

5 REGISTRATION PROCEDURES

BCT institutions will pre-register and register patients via the BCT website (www.breastcancertrials.org.au).

Patients will be recruited from investigators' clinical practices. Patients will sign a 'consent to screen' form at the pre-registration step. A separate written informed consent must also be signed by the patient and investigator prior to registration.

5.1 Pre-registration

1. Obtain written informed consent for pre-operative MRI scan, signed and dated by the patient and investigator.
2. Access the PROSPECT online registration system (www.breastcancertrials.org.au) and perform pre-registration. The data listed below will be collected:
   - Date of birth
   - Physical examination
   - Menopausal status (refer to appendix G)
   - Concurrent serious illnesses
   - Family history
   - Primary tumour receptor status (ER, PR and HER2 neu by IHC)
   - Biochemistry (eGFR)
   - Diagnostic imaging (mammogram and ultrasound)

   An email confirming that the pre-registration step has been successful and a patient pre-registration code number will be assigned.
3. Conduct the trial specific MRI and surgery. The MRI report and surgical report must be faxed to BCT (Fax 1300 138 136) and data entered in the online registration system.
4. Where requested, allow central radiology reviewers access to imaging (U/S, mammogram, and MRI) which confirms unifocal breast cancer, and, any additional suspicious lesions have been appropriately identified for further assessment (see figure 2).

5.2 Registration

1. Obtain written informed consent for participation in ANZ1002 PROSPECT, signed and dated by the patient and investigator.
2. Consent for tissue banking of the primary tumour will be sought to allow subsequent research studies.
3. Patients must be registered within 8 weeks after final excisional surgery.

4. Verify eligibility (refer to section 3) and confirm receipt of an 'eligible patient' notification email. Where central radiological review is being undertaken, the notification email will not be generated until the review is complete.
5. Access the ANZ1002 PROSPECT online registration system (www.breastcancertrials.org.au), identify the correct patient based on the pre-registration code number and perform registration.

5.3 Post registration

A patient registration number (Patient ID) will be supplied to acknowledge successful registration to the trial. Staff at the institution must enter the Patient ID on the baseline CRFs, submit these to BCT within 2 weeks of registration, and file the original forms in the patient CRF folder.

A forms due schedule will be provided by BCT. This schedule must be followed and CRFs must be submitted within two weeks of each study visit. The Study Calendar (refer to section 6.2) and forms due schedules must be filed in each patient's trial folder, as an aid to the correct timing of protocol assessments.

6 STUDY PROCEDURES

6.1 Required Evaluations

6.1.1 Pre-Surgery/Pre-registration

Patients willing to consider participation in the ANZ1002 PROSPECT study must have unifocal disease on mammography (refer to section 3) have histologically confirmed** ER+ and/or PR+ and/or HER2+ breast cancer, and have signed the screening consent to undergo a pre-operative MRI scan prior to being pre-registered.

** Oestrogen receptor and progesterone receptor status of invasive cancer will be assessed by immunohistochemistry on the diagnostic specimen. The IHC results will be reported as percentage of nuclei stained and a score of intensity from negative, weak, intermediate or high staining

- HER2 neu status will be assessed by immunohistochemistry and will be scored as follows[59]:
  - 0 or 1+ (HER2 negative No staining (0) or <10% of cancer cells show weak to moderate staining (1+)
  - 2+ (equivocal) <10% of cancer cells show strong complete membrane staining (rare) or 10–30% of cancer cells show weak to moderate complete membrane staining or strong cytoplasmic staining is present, making assessment of membrane staining difficult
  - 3+ (HER2 positive) >30% of cancer cells show strong, complete membrane staining without cytoplasmic staining and without staining of normal breast tissue (ASCO/CAP: 30% rather than 10%).

6.1.1.1 MRI protocol

Each site will nominate one MRI facility to undertake all study MRIs. All sites must agree to the study requirements for MRI protocols as outlined in this section.

MRI is not suitable for patients with any of the following (refer to section 3.2): pacemaker, implanted non-MRI compatible devices, cochlear implants, neurostimulators, insulin infusion pumps, (eGFR) <30 ml/min/1.73m^2.

Compatibility checks are required for: aneurysm clips, those with a history of metallic ocular foreign bodies, vascular coils, stents and filters, eye implants and heart valve replacements.

- If there is more than mild background parenchymal enhancement, the patient is not eligible for the study and will be managed according to the usual guidelines.
- If there are any suspicious lesions other than the known cancer, these are biopsied prior to or at surgery and managed appropriately (see section 6.1.3).
- If the additional lesions are not DCIS or invasive cancer, the patient is still potentially eligible for the trial.

Uniform scanning parameters will require women to be prone, with breasts placed in the MRI coils and minimal lateral compression to maintain immobilisation. The following settings will be used:

1. Pre-contrast

   Bilateral axial scans including T1 (3D acquisition) and T2 sequences one of which is not fat saturated. Isotropic voxel equal to or less than 1x1x1mm^3 for 3d sequences.

2. Dynamic contrast enhanced

   Contrast: 0.1mmol/kg body weight of a macrocyclic contrast agent administered intravenously preferably by injector. The dynamic sequence should be fat suppressed and preferably a 3D acquisition with isotropic voxel equal to or less than 1x1x1mm^3. Image acquisition should include a pre-contrast T1 weighted sequence, followed by at least 4 post contrast T1 weighted sequences. The first post-contrast sequence should be timed to coincide with the peak of contrast enhancement, usually in the first 90 seconds, the remaining sequences to follow every 90 seconds.

3. Images are to be presented in unsubtracted and temporal subtracted formats.

4. Enhancement kinetics reviewed on the scanner work-station or CAD work-station

5. BI-RADS[58] reporting system and double reporting by two experienced breast MR radiologists (at least one of whom is a chief investigator or associate investigator of the study). BI-RADS 3 lesions would ordinarily have a recommendation for 6 month follow up MRI scan. These lesions will be grouped with the BI-RADS 4 lesions and a tissue diagnosis is required.

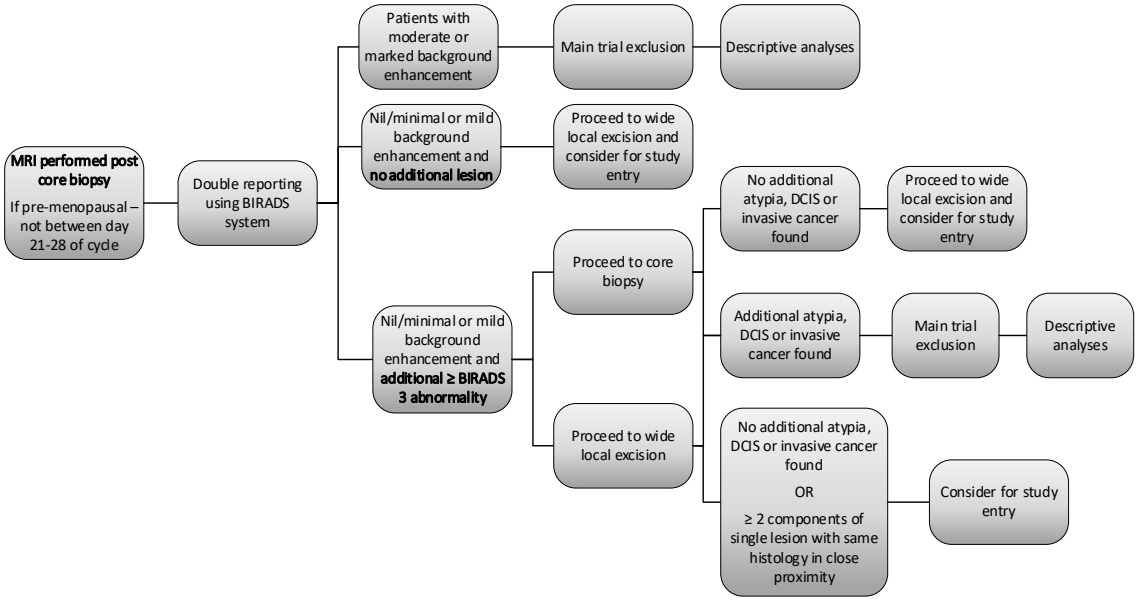
Background parenchymal enhancement will be assessed using the first post contrast series with subtracted and unsubstracted images. **Patients with moderate or marked parenchymal enhancement will be excluded.**

In those patients with no/minimal/mild background parenchymal enhancement, an additional BI-RADS 3-5 mass will require further investigation with US-guided MRI-directed core biopsy or excisional biopsy at primary surgery. Patients who have biopsy-proven additional malignant disease will be excluded.

In those patients with no/minimal/mild background parenchymal enhancement and additional BI-RADS 3-5 non-mass enhancement, a MRI guided biopsy or excisional biopsy at primary surgery will be performed and biopsy-proven additional malignant disease will be excluded.

In those patients with no/minimal/mild background parenchymal enhancement and additional BI-RADS 3-5 foci or focus, a MRI guided biopsy or excisional biopsy at primary surgery will be performed and biopsy-proven additional malignant disease will be excluded.

Figure 2 MRI Protocol



6.1.2 Central imaging review

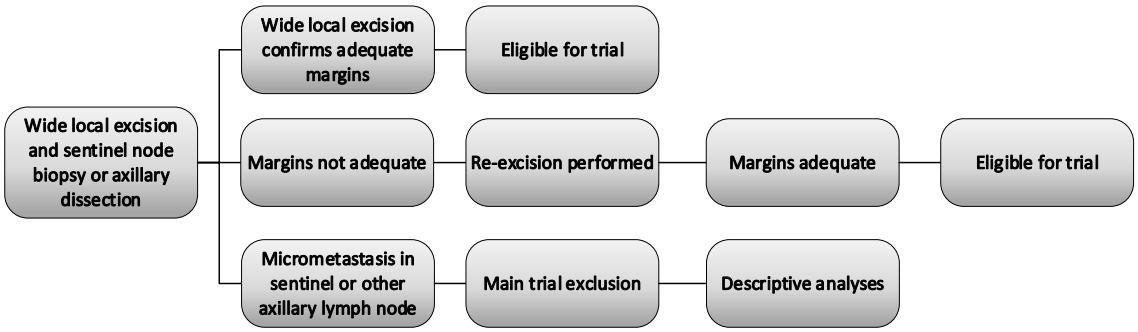
Each pre-registered patient will have the imaging undertaken for screening and staging (U/S, mammogram and MRI) centrally reviewed to confirm eligibility. Central radiology review will be undertaken by radiologists from Royal Melbourne Hospital. Findings and interpretations will be discussed between the site and central radiologists, however eligibility based on imaging will be determined by the central radiologists undertaking the review.

6.1.3 Surgery

6.1.3.1 Surgical Procedures

Patients will undergo wide local excision of the breast cancer and sentinel node biopsy or axillary dissection (in the case of failed or refused sentinel node biopsy). Where an additional mass has been identified by MRI, but not investigated by core biopsy, excisional biopsy at the time of primary surgery is required. The breast specimen shall be orientated in the operating room according to standard hospital protocols. Any intraoperative margin re-excision specimens shall be orientated to allow calculation of the true margin. The true margin is calculated by adding the initial margin to the width of re-excised tissue in the plane of the margin. If the invasive tumour (or DCIS) is within 2 mm of an inked radial margin and has not been re-excised intra-operatively, then this margin must be re-excised to achieve the required margin for the patient to be eligible for the trial. Superficial and deep margins of <2 mm for invasive cancer or DCIS are allowed if these margins are not involved and all breast tissue from the subcutaneous tissue or pectoralis fascia respectively are surgically removed and this is documented in the operative record.

Figure 3 Surgical Management



6.1.3.2 Pathological assessment

Each participating centre should identify a pathologist responsible for handling and reporting information derived from specimens of breast cancer.

Surgical specimens will be assessed according to guidelines from the National Breast and Ovarian Cancer Centre (The pathology reporting of breast cancer. A guide for pathologists, surgeons, radiologists and oncologists (3rd edition 2008)).

For patients pre-registered to ANZ1002 PROSPECT trial the following data must be documented in histopathology reports of breast surgical procedures, specifically:

- Invasive tumour size will be confirmed microscopically
- Resection margin distance ≤10 mm will be confirmed microscopically. Distance >10 mm will be recorded as >10 mm
- Lymphovascular invasion will be assessed histologically Immunohistochemistry with CD34 to highlight endothelial cells will be used insuspicious areas
- If not previously done on the diagnostic core, HER2 neu status must be assessed by ISH testing (using HER2 SISH or CISH). Fluorescence in Situ Hybridisation (FISH) will be used in equivocal cases
- Sentinel node biopsy specimens will have sentinel node(s) dissected from adipose tissue. Nodes will be sliced at 2mm interval and placed in a single cassette per node. 3 HE levels at 200 microns will be examined and 1 immunostain with Cam5.2 will be performed.
- Sentinel Nodes will be classified as
    1. negative
    2. isolated tumour cells (tumour cell focus <0.2 mm)
    3. micrometastasis (0.2-2 mm focus)
    4. metastatic focus >2 mm

- Axillary dissection specimens will have individual nodes dissected from adipose tissue and examined by H&E staining
- Ductal Carcinoma in Situ (DCIS)
  - DCIS will be assessed by histology
  - Immunostains with P63 and myosin heavy chain will be used to assist in separating in situ tumour from invasive tumour
  - Extensive DCIS (Extensive Intraductal Component (EIC)). Extensive DCIS is defined as invasive carcinoma with the following three components:
    - DCIS is present within the invasive tumour; and
    - DCIS within invasive tumour comprises more than 25% of the invasive tumour volume; and
    - DCIS exists beyond the margin of the invasive tumour

6.1.4 Post Surgery/Registration

Evaluations must be completed prior to registration unless otherwise specified in the Study Calendar in Section 6.2.

The data listed below will be collected via the Online Registration System:

- Confirmation ECOG performance status is <2
- Histopathology data pertaining to the primary tumour (refer to section 6.1.3.2)

Registered patients will receive systemic therapy as per usual guidelines, but will forego post-operative radiotherapy.

6.1.5 Follow up of patients not eligible for main study participation

See Appendices I and J for data to be collected.

6.1.6 Study visits/Procedures

All patients:

Pre-registration – pre-operative MRI scan (≤6 weeks prior to first excisional surgery).

Post- registration:

- Clinical review every 3 months for the first 6 months post final excisional surgery followed by:
- 6 monthly review for 5 years
- 12 monthly review until 10 years or until the final analysis, whichever occurs first
- A mammogram will be performed 6 months post final excisional surgery; annually thereafter
- A MRI will be performed 18 months post final excisional surgery

If a local recurrence is suspected on clinical examination or imaging, the diagnosis will be confirmed with percutaneous biopsy and management will be along usual guidelines, informed by the opinion of the multidisciplinary team at the institution. All suspected ipsilateral invasive recurrences must be reported to BCT on the Suspicion of Ipsilateral Invasive Recurrence (SIIR) form within 24 hours of suspicion. Investigations ordered on the grounds of patient reported findings, clinical palpation, routine imaging or positive cytology constitute suspicion, requiring the submission of the SIIR form. Once histology is available the outcome of the suspicion will be confirmed on the Follow Up (E) form and if necessary Ipsilateral Invasive Recurrence (IIR) forms.

6.1.7 Post-operative radiological surveillance

If the mammogram shows equivocal or suspicious changes, these will be investigated with ultrasound and ultrasound-guided or stereotactic core biopsy as clinically indicated.

If the MRI at 18 months shows any additional mass enhancement or non-mass enhancement or additional foci, these will be investigated with targeted ultrasound and ultrasound or MRI-guided core biopsy to diagnose or exclude local recurrence.

Any local recurrence will be managed with appropriate surgery with or without adjuvant radiotherapy, and the local recurrence must be promptly reported to BCT.

6.2 Study Calendar

	Pre-Registration Visit	Registration Visit	Study Visits				
Month		**0**	**3**	**6**	**12**	**18**	**24[8]**
Visit	**Screening**	**0**	**1**	**2**	**3**	**4**	**5**
Informed Consent[1] (Screening Consent)	+						
Informed Consent[1] (Main Consent)		+					
Age, ECOG PS, Medical history, BRCA Status and Cancer Australia risk grouping	+						
Physical Examination[2]		+	+	+	+	+	+
Anti-cancer therapy[3]		+	+	+	+	+	+
Biochemistry[4]	+					+	
MRI[5]	+					+	
Mammogram[6]	+			+		+	
Adverse Events[7]	+					+	

1 Informed consent initially obtained for pre-operative MRI. Once eligibility confirmed, informed consent obtained for study registration

2 Physical Examination. Refer to Section 6.1.5

3 Enter details of all anti cancer therapy e.g. hormonal therapy, chemotherapy on the case record form

4 Renal function test (UEC) and eGFR. Performed within 28 days prior to pre-operative MRI scan and repeated prior to 18 month MRI scan

5 MRI must be performed within 6 weeks prior to first breast surgery and at 18 months post final breast surgery. Pre-menopausal women must not have a MRI scan between days 21 and 28 of their menstrual cycle. Refer to Appendix G for menopausal status

6 Mammogram must have been performed within 3 months prior to first excisional surgery and breast density on mammogram should be reported.

7 Report Adverse Events related to MRI/contrast only

8 Patients will continue to be followed every 6 months from 12-60 months post final excisional surgery and annually for up to 10 years or until the final analysis, whichever occurs first

6.3 Prior and Concomitant Therapy

Systemic hormone replacement therapy (HRT) must be ceased within 4 weeks of histological diagnosis of breast cancer. Topical HRT for severe symptoms is at the discretion of the clinician but must be clearly documented.

Patients will be eligible for enrolment in other clinical trials, with prior approval from the Study Chair.

6.4 Study Discontinuation

Patients will remain on the study unless consent is withdrawn.

7 SAFETY AND ADVERSE EVENTS

7.1 Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a trial patient. An AE does not necessarily have a causal relationship with the treatment or trial patient. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with participation in a trial, whether or not related to that participation. This includes all deaths that occur while a patient is on a trial.

7.1.1 Adverse Event reporting for ANZ1002

Adverse Events related to the MRI procedure including MRI contrast only are to be reported. All other treatments/imaging are standard of care and therefore events are not to be reported to BCT.

Events due to breast cancer or its progression are study endpoints and are not categorised or reported as adverse events in this study.

As far as possible, each grade 1- 5 adverse event must be described by:

1. NCI-CTCAE (Version 4.0) terms – Common Terminology Criteria for Adverse Events (Refer to Appendix C).
2. Duration (start and end dates). The entire duration of the AE should be reported.
3. Severity Grade. The severity of each grade should be reported.
4. Whether the event was reported as a Serious Adverse Event (SAE).

Only adverse events that are NOT included in the NCI CTCAE v4.0 should be reported and graded under the "Other" adverse event within the appropriate category and graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening or disabling (Grade 4), or fatal (Grade 5) using the general definitions provided:

Table 2 Non-CTCAE severity grading

Grade	Severity	Description
1	Mild	Barely noticeable, does not influence functioning Causing no limitations of usual activities
2	Moderate	Makes participant uncomfortable, influences functioning Causing some limitations of usual activities
3	Severe	Severe discomfort, treatment needed Severe and undesirable, causing inability to carry out usual activities

4	Life threatening or disabling	Immediate risk of death
5	Fatal	Causes death of the participant

7.2 Serious Adverse Event (SAE)

Serious Adverse Events related to the MRI procedure including MRI contrast only are to be reported. All other treatments/imaging are standard of care and therefore events are not to be reported to BCT.

A SAE is any adverse event (experience) or reaction or any untoward medical occurrence that fulfils one of the following:

- Is fatal (results in death)
- Life threatening (Note: the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which could hypothetically have caused death had it been more severe)
- Required patient hospitalisation or prolongation of existing hospitalisation (Note: "inpatient hospitalisation" refers to an unplanned, overnight hospitalisation)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above

Events not considered to be serious adverse events are hospitalisations occurring under the following circumstances:

a) Planned before entry into the clinical trial for a pre-existing condition that is unrelated to the studied indication

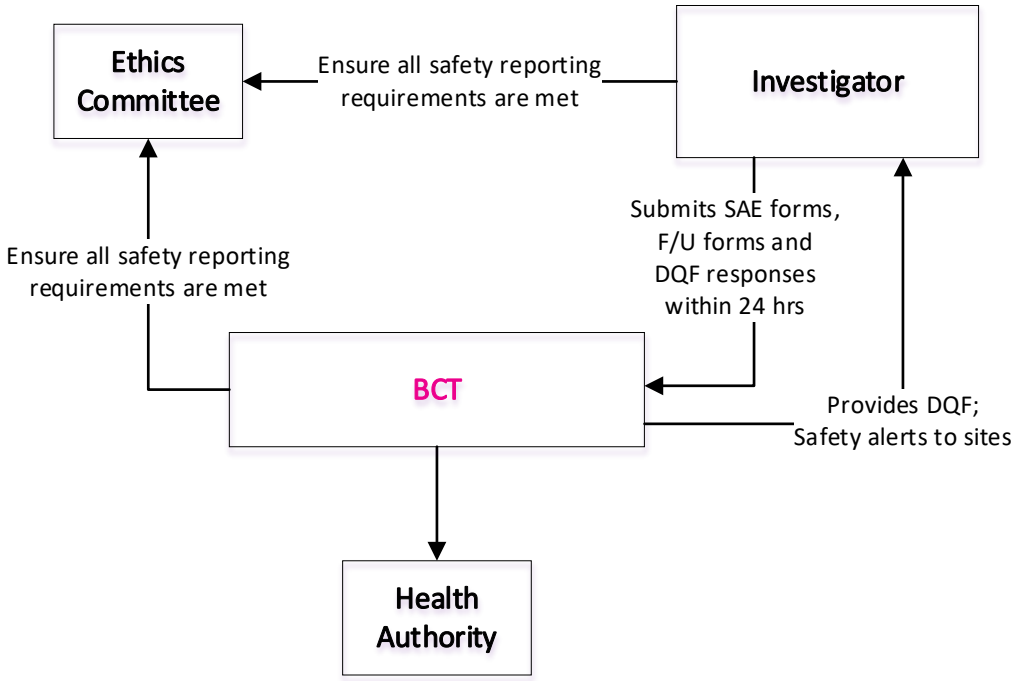
b) For elective treatment of a condition unrelated to the studied indication or its treatment

c) Emergency and/or outpatient hospitalisation not resulting in admission (unless fulfilling the criteria of serious given above)

d) Part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

e) Admission to a hospital or other institution for general care, not associated with any deterioration in condition

Figure 4 SAE reporting flowchart



Abbreviations:
DQF = Data query form prepared by BCT in order to clarify or collect more information regarding the SAE report
F/U form = Follow up to original SAE report
SAE form = Serious adverse event (SAE) report prepared by investigator

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalisation, but may jeopardise the patient or require intervention to prevent one of the outcomes listed in the definition above. These situations should usually be considered serious.

Follow up SAE information should be faxed to BCT within 24 hours of becoming aware of any change in the event. A new SAE form must be completed, stating that this is a follow up to a previously reported SAE and providing the date of the original report. The follow up information should be reported every 15 days until resolution of the event and detail the following:

a) whether the event has resolved or continues

b) if and how it was treated

c) whether the patient continued or withdrew from trial participation.

The follow up SAE form must be retained by the institution, and a copy held by BCT.

All SAEs shall be reported to the responsible HREC (and the RGO in the case of multi-centre research processes) by the local Principal Investigator at the institution where the SAE occurred. A copy of the report must also be provided to BCT (and Lead Investigator in the case or multi-centre research). Ethics acknowledgment of receipt of SAE notifications shall be filed at the local institution (and at the Lead Site in the case or multi-centre research).

SAE report summaries will be distributed to investigators biannually. In addition, they will be available on the BCT website (www.breastcancertrials.org.au).

7.3 Pregnancies

In the unlikely event that a pregnancy occurs during the trial, this must be reported by the investigator to BCT within 24 hours of learning of its occurrence. Pregnancy and pregnancy follow up should be reported on the Pregnancy Notification Form but any SAE experienced during pregnancy must be reported on the SAE form.

7.4 Procedures to be followed in the case of a medical emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the trial. Patients will be provided with a list of contacts involved in the trial at their site. A letter will be sent to each patient's GP notifying them of the patient's involvement in the trial.

8 TRIAL COORDINATION

This trial will report clinical data using the BCT Online Registration System and hard copy paper CRFs for trial data submission and SAE reporting.

Trial coordination procedures for this protocol will adhere to the ICH-GCP Guidelines and will be performed according to the ANZ1002 PROSPECT Study Coordinator Manual.

The trial is sponsored and coordinated by BCT. The trial has been endorsed by the BCT Scientific Advisory Committee.

8.1 Patient Identification

All patients screened for the trial will be entered on the online screening log and all pre-registered patients will be allocated a pre-registration number.

Each patient will be assigned a Registration Number (Patient ID) on registration to the trial. This number and the patient initials are to be entered on the CRFs.

8.2 Case Record Forms

The trial will be conducted using paper based CRF templates supplied by BCT. The CRFs are to be printed as required from the BCT website (www.breastcancertrials.org.au).

CRFs must be completed in accordance with the visit schedule and submitted by fax with supporting de-identified source data to the BCT on (+61) 1300 138 136.

CRFs are NOT to be mailed to BCT unless this procedure is specifically authorised. CRFs and source data should be readily available for review during scheduled audit visits. Further details on form completion and data submission requirements can be found in the ANZ1002 PROSPECT Study Coordinator manual.

8.3 Data Submission Schedule.

Patients entered to the main study are required to have data submitted according to the following:

- ONLINE: Pre-registration (PR1-4), Registration (A), Preoperative MRI (PreopMRI) and Surgery Forms (S) must be submitted prior to registration.
- CRF: Baseline (B form) must be submitted within 2 weeks of registration
- CRF: Follow Up (E Forms) must be submitted within 2 weeks of each protocol defined follow up visit
- CRF: SAE forms (refer to protocol section 7.2)

See Appendix J for data submission requirements for the pre-registered patient outcomes substudy.

8.4 Site Signature and Delegation of Authority Log

The names and periods of involvement of all trial personnel, including investigators, registrars and study coordinators must be recorded on the Site Signature and Delegation

of Authority Log. The PI or a Co-investigator will determine patient eligibility, obtain informed consent, plan trial treatment, make treatment related decisions, review patients at follow up visits according to the protocol and sign CRFs, including CRF segments. Registrars may be involved in these processes under the supervision of the PI or a Co-investigator.

8.5 Source Documents

All data recorded on CRFs must be able to be source data verified. Typical source documents include the following: progress notes in medical record, radiology reports, histopathology reports, haematology and biochemistry reports. Source data to verify major data points must be faxed to BCT on request.

8.6 Study Documents and Record Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, participant informed consent forms and documentation of ethics and regulatory approvals. BCT will provide investigators with the study-specific Investigator File to ensure sites file study documentation to meet GCP Essential Document requirements. The Investigator File must be kept up to date and be readily available at all times.

Trial regulatory information (including ethics correspondence and approvals) must be retained in the Investigator File in a secure storage facility for at least fifteen (15) years after the completion of the research and until BCT directs that the materials may be destroyed or sent to BCT.

Clinical records, including CRFs, all source documentation (containing evidence of trial eligibility, history and physical findings, laboratory data, results of consultations etc) must be retained in a secure storage facility for at least fifteen years after the completion of the research.

9 PATHOLOGY TISSUE COLLECTION

9.1 Tissue Banking

9.1.1 Primary Tumour (mandatory)

Submission of a sample from the primary tumour for tissue banking within one month of registration is mandatory. One de-identified tissue block from formalin fixed paraffin embedded (FFPE) biopsies of the primary tumour is to be sent to:

ANZ1002 PROSPECT Trial

Hunter Cancer Biobank

HMRI Building, Level 3 West

Lot 1 Kookaburra Circuit

New Lambton Heights NSW 2305One FFPE block is preferred however if a FFPE block cannot be forwarded for tissue banking, the following must be submitted:

a) 5 unstained four micron sections on coated slides or,

b) 5 unstained coated slides containing FNAB specimens

Specimens will be registered and tracked with the patient ID and local laboratory FFPE block number. If the banked specimen is required at any time for diagnostic purposes, it will be returned to the institution upon receipt of a written request.

All primary tumour tissue samples will be stored at the BCT Tissue Bank for use in future research projects to investigate various aspects of cancer. All future research on stored tissue will have ethics approval and will be conducted under the supervision of the BCT Scientific Advisory Committee. Research conducted on the tissue samples will not be used for commercial gain.

9.1.2 Ipsilateral Recurrence (mandatory)

All ipsilateral recurrences (invasive tumour and/or DCIS) which are proven by protocol definition (refer to 10.3.1) will be excised and a sample of the tissue must be provided to BCT for central pathology review. Samples must be forwarded to BCT within 1 month of the surgical procedure.

The following items are required:

Histopathology reports from the local recurrence

AND

1x FFPE block AND 2x unstained four micron sections on coated slides

OR if FFPE block is not available

7x unstained four micron sections on coated slides

Send to:

ANZ1002 PROSPECT Trial

Hunter Cancer Biobank

HMRI Building, Level 3 West

Lot 1 Kookaburra Circuit

New Lambton Heights NSW 2305

All reports, slides and blocks must be marked with the Patient ID number. Please ensure the blocks and slides are carefully packaged to avoid damage during transport.

The FFPE block from each ipsilateral recurrence will be catalogued and maintained in BCT Tissue Bank. The blocks will be available for prospective and retrospective studies approved by the BCT Scientific Advisory Committee and Human Research Ethics Committees.

The unstained slides (x2) from each local recurrence will be forwarded by BCT to the nominated central pathologist for review.

Central pathology review will include histopathological parameters (tumour type and grade, presence of DCIS and lymphovascular invasion), hormone receptors (oestrogen and progesterone receptors), and HER2 status. Testing for genes which may be inherited is not part of the central pathology review of this study.

If the banked specimen is required at any time for diagnostic purposes, it will be returned to the institution upon receipt of a written request.

10 STUDY MONITORING, AUDITING AND INSPECTING

10.1 Auditing and Inspecting

During the course of the study, BCT personnel, or any third party entitled by BCT, may conduct site audits. The investigator will provide direct access to source data/documents for trial related monitoring, audits, Human Research Ethics Committee review and any other applicable regulatory inspections.

10.2 Independent Data and Monitoring Committee (IDMC)

The BCT IDMC will review the information from interim analyses, accrual rate and local recurrence rate on an ongoing basis (every six months). The IDMC will provide recommendations to the Steering Committee, who will have responsibility for any final decisions about protocol stopping or modification.

11 STATISTICAL CONSIDERATIONS

11.1 Study design and hypothesis

The PROSPECT trial is a phase II single arm clinical trial using magnetic resonance imaging (MRI) to select patients with early breast cancer for omission of radiotherapy. The hypothesis is that MRI in association with clinical and pathological features will allow identification of truly localized early breast cancer, for which omission of RT after wide excision is appropriate.

11.2 Study endpoints and Data Analyses

11.2.1 Analysis of the primary endpoint

The primary analysis will include all registered patients.

Primary endpoint:

- Ipsilateral invasive recurrence rate (IIR) in the breast at 5 years follow up from the date of definitive excisional surgery.

It is considered that a IIRR of 5% at 5 years would be acceptable, while a IIRR of >7% at 5 years would mean that the hypothesis is not supported.

Based on these numbers, the objective is to estimate the IIRR in participants with low risk breast cancer who do not receive radiotherapy. An estimate of an overall IIRR of 5% would be clinically acceptable and based on 200 participants; this would have 90% chance of declaring a true recurrence rate of <7%. The expected number of participants who are HER2 positive to be recruited is 30-35. The expected number of participants who are HER2 negative to be recruited is 165-170. The sample size for this study is 200 registered participants. The main efficacy analysis is planned after the 100th registered subject has reached 5 years of follow up. Efficacy data will also be reviewed after the 100th registered subject has reached 2 years of follow up.

11.2.2 Safety analysis and stopping rules

During the recruitment phase of the trial, safety analyses will be conducted to determine whether subject accrual to each cohort should continue or cease. Cessation of subject accrual will occur if an unacceptable rate of ipsilateral invasive recurrence is detected. Safety analyses will be performed on the two HER2 cohorts (positive and negative) and in two cohorts of participants based on tumour grade (high grade and non-high grade). In the first 46 participants in each cohort, a 7% IIRR would require no ipsilateral invasive recurrences while one ipsilateral invasive recurrence would be consistent with up to a 10% event rate (with 95% confidence). During the early part of recruitment each local recurrence will have a large effect on the IIRR confidence limits than a recurrence during the latter part of recruitment. For example, in the HER2 negative cohort, if one ipsilateral invasive recurrence is observed in the first 10 participants but no other ipsilateral invasive recurrences occur in the subsequent 150 participants enrolled, overly restrictive stopping rules would result in premature and

unnecessary closure of accrual. Therefore, it is thought that stopping the study after one ipsilateral invasive recurrence in the first 46 participants would be premature to adequately address the scientific question. So for the first 46 participants, a 10% recurrence rate boundary is appropriate. Thus, if 2 or more local recurrences occur in the first 46 participants in each cohort, accrual to that particular cohort will cease. Similarly, if 3 or more ipsilateral invasive recurrences are observed in the first 90 participants in each cohort, accrual to that particular cohort will cease. For 90, 110, 130 and 150 participants the boundaries (see Tables 3 and 4) assume a IIRR in the HER2 negative population consistent with 7% or lower.

Due to the lower expected number of HER2 positive participants, accrual of participants who are HER2 positive will be stopped if at any time the cumulative number of ipsilateral invasive recurrences observed in the 5 year period exceeds 1, i.e. 2 or more ipsilateral invasive recurrences are observed. In the event that the accrual of HER2 positive participants is higher than anticipated, accrual to this cohort will proceed to 50 participants to allow for increased precision of IIRR. The rules for stopping accrual continue to apply so that if at any time the number of ipsilateral invasive recurrences exceeds 1, then accrual to the HER2 positive cohort will cease.

As 2 ipsilateral invasive recurrences are the first threshold for possible cessation of subject accrual, safety analysis and a decision on continuing or ceasing subject accrual will occur at the time of detection of the second local recurrence and at the time of all further ipsilateral invasive recurrences.

The following tables give the number of ipsilateral invasive recurrences required to rule out a ≥10% rate up to 46 participants and after 46 participants, a ≥7% rate.

Table 3 Stopping rules for HER2+ and HER2- cohorts

Rules for stopping accrual based on the number of ipsilateral invasive recurrences observed in HER2+ and HER2- cohorts:

Number of participants accrued in each cohort						
	Any	46	90	110	130	150
HER2+	≥ 2	-	-	-	-	-
HER2-	-	≥2*	≥3‡	≥4‡	≥5‡	≥6‡

*Unacceptable IIRR of 10% is consistent with this result

‡ Unacceptable IIRR of 7% is consistent with this result

Table 4 Stopping rules for high grade and non-high grade cohorts

Rules for stopping accrual based on the number of ipsilateral invasive recurrences observed in high grade and non-high grade cohorts:

Number of participants accrued in each cohort						
	46	90	110	130	150	
High grade	≥2*	≥3‡	≥4‡	≥5‡	≥6‡	
Non-high grade	≥2*	≥3‡	≥4‡	≥5‡	≥6‡	

*Unacceptable IIRR of 10% is consistent with this result

‡ Unacceptable IIRR of 7% is consistent with this result

11.2.3 Analysis of the Secondary Endpoints

Secondary endpoints:

1. Ipsilateral invasive recurrence rate in the breast at 10 years
2. Ipsilateral DCIS recurrence rate in the breast at 5 and 10 years
3. Regional recurrence rate at 5 and 10 years
4. Distant recurrence rate at 5 and 10 years
5. Contralateral breast cancer rate at 5 and 10 years
6. Breast-cancer specific survival rate at 5 and 10 years
7. Overall survival rate at 5 and 10 years

Analysis of ipsilateral invasive recurrence will also be performed when the 100th subject enrolled reaches 10 years of follow up from the date of definitive excisional surgery. Regional and distant recurrence rate will be analysed when the 100th subject enrolled reaches 5 years and 10 years of follow up from the date of definitive excisional surgery. Time to event outcomes (breast cancer specific and overall survival at 5 and 10 years) will be described using Kaplan Meier curves. The potential impact of baseline factors on recurrence and time to recurrence will be examined using appropriate regression methods (logistic, proportional hazards).

11.2.4 Other descriptive analyses

The entire cohort of patients undergoing pre-operative staging MRI will be included in descriptive analyses of:

- A substudy of the outcome of MRI at breast cancer diagnosis, the impact of MRI and the accuracy of MRI (Appendix H).

- An economic evaluation to determine the potential cost-effectiveness of implementing a protocol where women with cT1cN0 hormone receptor-positive and/or HER2 positive early stage breast cancer undergo a pre-surgical MRI (and for those women where the MRI clearly shows no synchronous cancer lesions radiotherapy is omitted) compared to standard practice (no MRI and all women receive radiotherapy (Appendix I).
- A substudy of outcomes of the patients who underwent MRI but were deemed unsuitable for inclusion in the main study who consent to follow up (Appendix J).
- A substudy (Appendix K) to:
  - Conduct sequencing of the index and subsequent lesions to determine whether they are true recurrences or whether they are independent lesions
  - Analysis of the index lesion where there has been a subsequent event using the PAM50 assay, to determine whether it may identify those at high risk of recurrence.

11.2.5 Accrual rate

Average of 22 patients per year over 9 years.

11.3 Ipsilateral invasive, ipsilateral DCIS, regional, distant recurrence definitions

The date that a suspicious ipsilateral invasive, ipsilateral DCIS, regional or distant breast cancer recurrence is first suspected and the date that a recurrence is confirmed (per the "acceptable" criteria listed below) will be collected to define and analyse the primary and secondary endpoints.

11.3.1 Ipsilateral invasive recurrence

Ipsilateral invasive recurrence is defined as an invasive recurrence (with or without in-situ tumour) in any soft tissue of the ipsilateral conserved breast or skin.

- Acceptable for recurrence in ipsilateral conserved breast: positive histology.
- Acceptable for recurrence in skin: positive histology
- Suspicious: positive cytology or a visible or palpable lesion.

The diagnosis of LCIS either in the ipsilateral breast or in the contralateral breast is not considered an endpoint for this trial, but should be reported on the case record form.

11.3.2 Ipsilateral DCIS Recurrence

Ipsilateral DCIS recurrence is defined as the diagnosis of any DCIS occurrence (without associated invasive carcinoma) in any soft tissue of the ipsilateral conserved breast.

- Acceptable for diagnosis of DCIS in ipsilateral conserved breast: positive histology.
- Suspicious: suspicious mammographic or MRI findings.

11.3.3 Regional Recurrence

Regional recurrence is defined as a tumour recurrence in the ipsilateral axillary lymph nodes, extranodal soft tissue of the ipsilateral axilla, ipsilateral internal mammary lymph

nodes, and/or ipsilateral supraclavicular lymph nodes. Regional recurrence does not include supraclavicular lymph nodes or tumour in the opposite breast (see section 11.3.4 for information on contralateral breast cancer).

- Acceptable: positive cytology or histology
- Suspicious: a visible or palpable lesion or evidence of new lesions by CT or MRI without a benign aetiology

11.3.4 Distant Recurrence

Recurrence in all areas other than those defined above are considered distant metastases. The following criteria apply:

11.3.4.1 Bone marrow

- Acceptable: positive cytology or histology.
- Suspicious: unexplained depression of peripheral blood counts and/or a leucoerythroblastic blood picture.

11.3.4.2 Lung

- Acceptable: positive cytology or histology, or a positive CT or MRI without obvious benign aetiology, or evidence of progressive disease. (Progressive disease is confirmed by two X-rays with the second showing worsening disease.)
- Suspicious: new radiological lesion(s).

11.3.4.3 Pleura

- Acceptable: positive cytology or histology.
- Suspicious: new pleural effusion.

11.3.4.4 Bone

- Acceptable: positive cytology or histology or a positive X-ray, MRI, or CT or bone scan with new multiple lesions and no obvious benign aetiology.
- Suspicious: skeletal symptoms or positive scan showing only one new lesion (until confirmed by other imaging study or biopsy).

11.3.4.5 Liver

- Acceptable: positive cytology or histology, or positive CT or MRI without an obvious benign aetiology, or evidence of progressive disease by ultrasound or CT. (Progressive disease in this case is confirmed by two ultrasounds or CTs with the second showing worsening disease.)
- Suspicious: any two of the following: hepatomegaly on physical examination, equivocal ultrasound and abnormal liver function test.

11.3.4.6 Central nervous system

- Acceptable: positive cytology or histology. Positive MRI or CT when the clinical picture is suspicious.
- Suspicious: any other clinical findings suggestive of this diagnosis.

11.3.4.7 Distant lymph nodes

- Acceptable: positive cytology or histology
- Suspicious: evidence of enlarged lymph nodes by physical exam, or enlarged lymph nodes in CT or MRI, or progressive disease by physical exam without an obvious benign aetiology.

11.3.4.8 Other sites

- Acceptable: positive cytology or histology or evidence of progressive disease if only indirect means of diagnosis were used (e.g., X-ray).
- Suspicious: clinical and radiological evidence of a tumour.

11.3.5 Contralateral breast cancer

The first contralateral invasive breast cancer must be reported on the SPM form if it occurs at any time during the study

- Acceptable: positive cytology or histology.
- Suspicious: a visible or palpable lesion, suspicious mammogram, ultrasound, or MRI.

The diagnosis of LCIS and DCIS in the contralateral breast is not considered an endpoint for this trial, but should be recorded on the case record form.

11.4 Second (non-breast) primary

Any positive diagnosis of a second (non-breast) malignancy other than a basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, or bladder cancer in situ should be reported on the case record form (SPM).

11.5 Death

All deaths must be reported. The date and cause of death must be reported on the case record form (DR).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Required Documents

Prior to initiating this trial, the Principal Investigator at each institution will ensure that all required regulatory and other associated documentation is forwarded to BCT.

12.1.1 Submission of Regulatory Documents

All regulatory documents are to be submitted to BCT. Once BCT has received complete and accurate documents from a participating institution, the institution will be activated to commence pre-registration and registration of patients.

12.2 Human Research Ethics Committee (HREC)

All protocols and the Participant Information Sheet and Consent Forms must have the approval of a properly constituted ethics committee. The approving HREC must provide a written, signed letter/form which must specify approval for the designated investigator, the trial protocol (identifying protocol title and version date), and of the Participant Information Sheet and Consent Form (identifying version date). Additionally, all recruitment materials must be reviewed by the approving HREC. Documentation of ethics committee approval must be sent to the BCT.

The Principal Investigator (or Coordinating Investigator for multi-centre ethics submissions) is responsible for informing the approving HREC of any amendment to the protocol.

The Principal Investigator (or Coordinating Investigator) must submit progress reports to the HREC according to the committee regulations and guidelines. The approving HREC must also be notified of all reports of SAEs from the trial centres.

12.3 Informed Consent

The Participant Information Sheet and Consent Forms (screening and main) must be reviewed and approved by BCT and the approving HREC prior to trial initiation. For multi-centre ethics submissions, the lead HREC will review the template Participant Information Sheet and Consent Forms. Any subsequent changes to these documents (other than local site identifiers) must be approved by BCT prior to submission to the HREC. Template Participant Information and Consent Forms are provided in Appendix A.

Informed consent from each patient must be obtained prior to initiating any trial procedures in accordance with the International Conference on Harmonisation for Good Clinical Practice (ICH-GCP). All potential trial participants will be given a copy of the HREC approved Participant Information Sheet and Consent Forms to read and discuss with family, GP etc. The investigator will explain all aspects of the trial in lay language and answer all questions regarding the trial.

If the patient decides to participate in the trial, she will be asked to sign the Informed Consent documents (screening initially and if eligible following screening then the

main). One copy of the Participant Information Sheet and signed Informed Consent must be given to the patient to keep and one copy must be retained in the institutional Investigator File. The completed and signed Informed Consent documents for all patients at the institution must be available in the case of data audits. Patients who refuse to participate or who withdraw from the trial will be treated without prejudice.

Regarding the substudy of outcomes of the patients who underwent MRI but were deemed unsuitable for inclusion in the main study, patients will be asked to sign the relevant Informed Consent document. Those patients who refuse consent, or decline to complete the consent, will not have additional information included, beyond the details collected as part of the screening aspect of the study to which they have already consented. They will be reported as 'refused consent' for this additional information.

A request to waive consent will be submitted to HREC for those patients who have died in the intervening time, those who are unable to provide informed consent due to mental deterioration and for those who are unable to be contacted. For these patients, information available within the medical records will be used in the study.

12.4 Participant Data Protection

BCT uses personally-identifiable information to conduct research to improve health, care and services. As a non-profit organisation, BCT ensures that it is in the public interest when personally-identifiable information from participants is used in their research; participants' data is used in ways needed to conduct and analyse the research study. Participants' rights to access, change or move their information are limited, as BCT needs to manage their information in specific ways for the research to be reliable and accurate. If participants withdraw from the study their information already collected will be retained. To safeguard participants' rights, BCT will use the minimum personally-identifiable information possible.

The Participant Information Sheet and Consent Forms will explain that trial data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. The patients' names will not be recorded in the database. The Participant Information Sheet and Consent Forms will also explain that for data verification purposes, authorised representatives of BCT, a regulatory authority, or a HREC may require direct access to parts of the hospital or practice records relevant to the trial, including patients' medical histories.

12.4.1 Notification of Personal Data Breach

A data breach occurs when personal information held by BCT about an Australian participant is lost or subjected to unauthorised access or disclosure. Notification is required where the data breach is an eligible data breach i.e. likely to result in serious harm to a participant e.g. to their physical, emotional or mental well-being, cause economic or financial harm, or damage to their reputation.

Data breaches will be reported according to applicable legislation.

12.5 Modification of the Protocol

Any modifications to the protocol which may impact on the conduct of the trial, potential benefit of the patient or may affect patient safety, including changes to trial objectives, trial design, patient population, sample sizes, trial procedures, or significant administrative aspects will be formally documented by an amendment to the protocol. Protocol amendments must be submitted to the approving HREC for review and approval.

12.6 Ethical Conduct of the Trial

This trial will be conducted in compliance with the protocol, the Declaration of Helsinki, International Conference on Harmonisation for Good Clinical Practice (ICH-GCP), and the applicable regulatory requirements.

This study is being conducted by doctors who are members of Breast Cancer Trials (BCT) which conducts research throughout Australia and New Zealand to help develop better ways of preventing, diagnosing and treating breast cancer. No member of the research team will obtain any financial benefit from their involvement in this study.

BCT is providing financial support for the conduct of this study.

12.7 Publication and Data Sharing

Publications and presentations resulting from this study will comply with recognised ethical standards concerning publications and authorship, including ICMJE Recommendations, established by the International Committee of Medical Journal Editors (http://icmje.org/recommendations/). Furthermore, publications and any kind of presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the BCT Publication Policy.

Study results will be communicated to participants, if appropriate, following publication of the main study results and in accordance with applicable BCT Procedures. Researchers may apply for access to study data, if appropriate, as per applicable BCT Procedures and the study Data Management Plan.

13 INSURANCE

BCT has Clinical Trials Liability Insurance for the trial. All persons, acting on behalf of the Named Insured, are covered as additional insured.

This insurance does not cover any liability resulting from medical malpractice and includes the territories of Australia and New Zealand.

Patients, who may suffer injuries as a result of trial participation, should report them immediately to their doctor.

Compensation procedures will be based on principles consistent with the 'Guidelines for Compensation for Injuries Resulting from Participation in a Company-sponsored Clinical Trial' published by Medicines Australia.

14 REFERENCES

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005 Dec 17;366(9503):2087-106.
2. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 2000 May 20;355(9217):1757-70.
3. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):971-7.
4. Godinez J, Gombos EC, Chikarmane SA, Griffin GK, Birdwell RL. Breast MRI in the evaluation of eligibility for accelerated partial breast irradiation. AJR Am J Roentgenol. 2008 Jul;191(1):272-7.
5. Tendulkar RD, Chellman-Jeffers M, Rybicki LA, Rim A, Kotwal A, Macklis R, et al. Pre-operative breast magnetic resonance imaging in early breast cancer: implications for partial breast irradiation. Cancer. 2009 Apr 15;115(8):1621-30.
6. Al-Hallaq HA, Mell LK, Bradley JA, Chen LF, Ali AN, Weichselbaum RR, et al. Magnetic resonance imaging identifies multifocal and multicentric disease in breast cancer patients who are eligible for partial breast irradiation. Cancer. 2008 Nov 1;113(9):2408-14.
7. .Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002 Oct 17;347(16):1233-41.
8. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 1989 Mar 30;320(13):822-8.
9. Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985 Mar 14;312(11):665-73.
10. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, 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 Oct 17;347(16):1227-32.
11. van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. J Natl Cancer Inst Monogr. 1992(11):15-8.

12. Blichert-Toft M. Breast-conserving therapy for mammary carcinoma: psychosocial aspects, indications and limitations. Ann Med. 1992 Dec;24(6):445-51.
13. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer. 2001 Jul 1;92(1):172-80.
14. Bernier J. Potential risks and benefits of radiation therapy as adjuvant treatment in patients with low-risk carcinoma of the mammary gland: taking cutaneous postradiation angiosarcoma as an opportunity for a critical appraisal of postoperative radiotherapy. Ann Oncol. 2007 Apr;18(4):619-21.
15. Billings SD, McKenney JK, Folpe AL, Hardacre MC, Weiss SW. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. Am J Surg Pathol. 2004 Jun;28(6):781-8.
16. Fodor J, Orosz Z, Szabo E, Sulyok Z, Polgar C, Zaka Z, et al. Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature. J Am Acad Dermatol. 2006 Mar;54(3):499-504.
17. Kunkler IH, Prescott RJ, Williams LJ, King CC. When may adjuvant radiotherapy be avoided in operable breast cancer? Clin Oncol (R Coll Radiol). 2006 Apr;18(3):191-9.
18. Kunkler I. PRIME II breast cancer trial. Clin Oncol (R Coll Radiol). 2004 Oct;16(7):447-8.
19. Kunkler I. Impact of Breast Radiotherapy on Quality of Life in Older Patients: A Phase III Trial. Clin Oncol (R Coll Radiol). 2007 Apr;19(3 Suppl):S12-3.
20. Hughes K, Schnaper, LA, Berry, D. Lumperctomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer:a report of further follow up. Breast Cancer Res Treat. 2006;100(Suppl 1):S8.
21. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70.
22. Fisher B, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol. 2002 Oct 15;20(20):4141-9.
23. Holli K, Hietanen P, Saaristo R, Huhtala H, Hakama M, Joensuu H. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow up results of a randomized trial. J Clin Oncol. 2009 Feb 20;27(6):927-32.
24. Tinterri C, Gatzemeier W, Zanini V, Regolo L, Pedrazzoli C, Rondini E, et al. Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: a prospective randomised multicentre trial. Breast. 2009 Dec;18(6):373-7.
25. Blamey R, Chetty, U, George, D, Bagtes, T. Radiotherapy and/or tamoxifen after conserving surgery for breast cancers of excellent prognosis:BASO trial. Eur J Cancer. 2008(S6):55.

26. Blamey R, Chetty, U, George, D, Morgan, C, Mitchell, C. Update of the BASO II trial of primary treatment of tumours of excellent prognosis. European Journal of Cancer. 2004 2004;Suppl 2:161.
27. Kunkler IH, Williams L, Prescott R, King C. Effects of radiotherapy and surgery for early breast cancer. Lancet. 2006 May 20;367(9523):1653-4; author reply 4-5.
28. Kaufmann M, Morrow M, von Minckwitz G, Harris JR. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer. Jan 19;116(5):1184-91.
29. Neri A, Marrelli D, Rossi S, De Stefano A, Mariani F, De Marco G, et al. Breast cancer local recurrence: risk factors and prognostic relevance of early time to recurrence. World J Surg. 2007 Jan;31(1):36-45.
30. Locker AP, Ellis IO, Morgan DA, Elston CW, Mitchell A, Blamey RW. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. Br J Surg. 1989 Sep;76(9):890-4.
31. Touboul E, Buffat L, Belkacemi Y, Lefranc JP, Uzan S, Lhuillier P, et al. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. Int J Radiat Oncol Biol Phys. 1999 Jan 1;43(1):25-38.
32. Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? Radiother Oncol. 2009 Jan;90(1):14-22.
33. Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol. 2009 Dec 1;27(34):5700-6.
34. Nguyen PL, Taghian AG, Katz MS, Niemierko A, Abi Raad RF, Boon WL, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol. 2008 May 10;26(14):2373-8.
35. Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, et al. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med. 2007 Mar 29;356(13):1295-303.
36. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer. 1985 Sep 1;56(5):979-90.
37. Anastassiades O, Iakovou E, Stavridou N, Gogas J, Karameris A. Multicentricity in breast cancer. A study of 366 cases. Am J Clin Pathol. 1993 Mar;99(3):238-43.
38. Lagios MD. Multicentricity of breast carcinoma demonstrated by routine correlated serial subgross and radiographic examination. Cancer. 1977 Oct;40(4):1726-34.
39. Egan RL. Multicentric breast carcinomas: clinical-radiographic-pathologic whole organ studies and 10-year survival. Cancer. 1982 Mar 15;49(6):1123-30.

40. Schwartz GF, Patchefsky AS, Feig SA, Shaber GS, Schwartz AB. Clinically occult breast cancer. Multicentricity and implications for treatment. Ann Surg. 1980 Jan;191(1):8-12.
41. Rosen PP, Fracchia AA, Urban JA, Schottenfeld D, Robbins GF. "Residual" mammary carcinoma following simulated partial mastectomy. Cancer. 1975 Mar;35(3):739-47.
42. Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol. 2004 Oct;183(4):1149-57.
43. Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet. 2007 Aug 11;370(9586):485-92.
44. Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008 Jul 1;26(19):3248-58.
45. Yabuuchi H, Kuroiwa T, Kusumoto C, Fukuya T, Ohno S, Hachitanda Y. Incidentally detected lesions on contrast-enhanced MR imaging in candidates for breast-conserving therapy: correlation between MR findings and histological diagnosis. J Magn Reson Imaging. 2006 Apr;23(4):486-92.
46. Bedrosian I, Mick R, Orel SG, Schnall M, Reynolds C, Spitz FR, et al. Changes in the surgical management of patients with breast carcinoma based on pre-operative magnetic resonance imaging. Cancer. 2003 Aug 1;98(3):468-73.
47. Mann RM, Hoogeveen YL, Blickman JG, Boetes C. MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat. 2008 Jan;107(1):1-14.
48. Caramella T, Chapellier C, Ettore F, Raoust I, Chamorey E, Balu-Maestro C. Value of MRI in the surgical planning of invasive lobular breast carcinoma: a prospective and a retrospective study of 57 cases: comparison with physical examination, conventional imaging, and histology. Clin Imaging. 2007 May-Jun;31(3):155-61.
49. Onesti JK, Mangus BE, Helmer SD, Osland JS. Breast cancer tumor size: correlation between magnetic resonance imaging and pathology measurements. Am J Surg. 2008 Dec;196(6):844-48; discussion 9-50.
50. Kepple J, Layeeque R, Klimberg VS, Harms S, Siegel E, Korourian S, et al. Correlation of magnetic resonance imaging and pathologic size of infiltrating lobular carcinoma of the breast. Am J Surg. 2005 Oct;190(4):623-7.
51. Mann RM. The effectiveness of MR imaging in the assessment of invasive lobular carcinoma of the breast. Magn Reson Imaging Clin N Am. May;18(2):259-76, ix.

52. Turnbull L, Brown, S, Olivier, C, Dre, P, Napp, V, Hanby, A, Brown, J. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. The Lancet. 2010;375(9714):563-71
53. Solin LJ, Orel SG, Hwang WT, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 2008 Jan 20;26(3):386-91.
54. Fischer U, Zachariae O, Baum F, von Heyden D, Funke M, Liersch T. The influence of pre-operative MRI of the breasts on recurrence rate in patients with breast cancer. Eur Radiol. 2004 Oct;14(10):1725-31.
55. Fischer U, Baum F, Luftner-Nagel S. Pre-operative MR imaging in patients with breast cancer: pre-operative staging, effects on recurrence rates, and outcome analysis. Magn Reson Imaging Clin N Am. 2006 Aug;14(3):351-62, vi.
56. Hwang N, Schiller DE, Crystal P, Maki E, McCready DR. Magnetic resonance imaging in the planning of initial lumpectomy for invasive breast carcinoma: its effect on ipsilateral breast tumor recurrence after breast-conservation therapy. Ann Surg Oncol. 2009 Nov;16(11):3000-9.
57. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010 Jun 1;28(16):2784-95.
58. Reston V, editor. Breast imaging reporting and data system, BI-RADS: MRI. 1st ed: American College of Radiology; 2003.
59. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007 Jan 1;25(1):118-45.

APPENDIX A: Participant Information Sheet and Informed Consent Templates (Screening and Main)

Headed with Institution's name or on Institution's Letterhead

Participant Information and Screening Consent Form

Version 2: 1st December 2013

Project Title: ANZ 1002: Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial (PROSPECT)

Institution conducting study: [enter name of institution]

Principal Investigator: [enter name of PI]

Associate Investigators: [enter name of AI's]

This Patient Information Sheet and Consent Form is seven pages long. Please ensure you have all the pages.

1. Introduction

You are invited to take part in a research study called PROSPECT. This is because your breast cancer may be localised to one area in the breast and therefore may not need radiotherapy after surgery.

This document is a screening consent form. It provides information about one of the tests needed to check if the PROSPECT study is suitable for you – a process called 'screening'. It asks for your consent (permission) so that a magnetic resonance imaging scan (called a MRI scan) can be performed before your surgery. We would also like to ask for your consent to allow researchers to collect data from you even if the main study (PROSPECT) is not suitable for you.

2. Purpose and background

This study is being conducted by the Australia and New Zealand Breast Cancer Trials Group (ANZBCTG). The ANZBCTG is comprised of doctors and researchers throughout Australia and New Zealand who are actively involved in research to help develop better ways of diagnosing and treating breast cancer. The purpose of the PROSPECT study is to determine if some women with early breast cancer can avoid radiotherapy treatment after breast surgery.

Magnetic resonance imaging (MRI) is a common procedure that uses a strong magnetic field to produce an image. In this study MRI will be used in a new way – to scan the breast prior to surgery. MRI sometimes shows a small breast cancer not seen on mammogram or ultrasound examination. When MRI has been used at the time of breast

cancer diagnosis extra abnormalities are sometimes found. The result may be that more extensive surgery is performed.

Agreeing to have a MRI scan does not automatically mean that you will participate in the PROSPECT study. If the results of the MRI scan and the tests of the cancer tissue taken during surgery show that the study may be suitable for you, your doctor will ask you to review and sign a separate information and consent form, which provides full details of this study. You must sign this separate information and consent form before you can take part in the main PROSPECT study. This separate information and consent form is available now if you wish to see it.

Your doctor will discuss the alternative treatments available if the PROSPECT study is not suitable for you.

3. What does screening for this study involve?

MRI screening procedure

If you consent to screening you will have a MRI scan. Prior to the MRI scan, a blood sample (about 1 tablespoon) will be collected to test your kidney function.

A MRI scan is a procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal tissue and breast cancer tissue.

The picture to the left is an example of a MRI machine.

A dye called a 'contrast' will be used in the MRI scan. The dye helps to show any abnormalities that may be present in your breasts. Before the MRI is done, a needle will be inserted into a vein in your hand or arm and the dye will be injected through this needle and into your body. When the contrast is injected, it is normal to feel coolness and a flushing sensation for a minute or two. The needle may cause you some discomfort when it is inserted and when it is removed you may experience some bruising. There is also a very small chance of infection of your skin at the site of the needle insertion.

Apart from the contrast injection, the MRI itself is a painless procedure. You will be required to lie still as the bed moves you into the narrow chamber of the MRI machine and the scan is undertaken.

Breast Tissue Biopsy

If a tissue abnormality is shown on the MRI scan, a piece of the abnormal tissue might be taken (this is called a biopsy). This would be performed either as a separate procedure before your scheduled breast surgery, or during your scheduled breast surgery.

Additional Information Collection

We will collect some information from you even if you are unable to participate in the main PROSPECT study. The data we would like to collect is listed below:

- General (e.g. age, menopausal status, family history)
- Imaging and Pathology Results (results from your mammograms, MRI scans and the results from a biopsy (if this is required).
- Surgery information (e.g. the type and size of cancer, whether any additional cancers were found during surgery and whether any cancer cells were present in nodes in your arm pits)

All information collected for this research study that can identify you will remain confidential and will only be used for the research purposes stated in this document. It will only be disclosed with your permission, except as required by law.

4. What will happen to my test samples?

Your blood samples will be tested at the hospital pathology department and will then be destroyed.

If a tissue biopsy is performed during the screening process, this tissue will be stored and managed as per standard hospital practice. It will not be used for research purposes.

5. What are the possible risks?

Possible risks from the dye (contrast):

<u>Common side effects (experienced in less than 1 in 20 patients)</u>

- headache
- nausea or vomiting
- local reaction around the injection site, namely, pain, coldness, warmth, burning sensation

Mostly these are mild and short-lived.

<u>Uncommon side effects (experienced in less than 1 in 100 patients)</u>

- Pain (e.g. chest, back, pelvis, teeth)
- Flu like symptoms (e.g. fever, tiredness, weakness, chest tightness, shivering, generalised feeling of warmth or coldness, throat irritation, running nose, sneezing, shortness of breath or wheezing, cough)
- Gastrointestinal (e.g. abdominal pain, constipation, diarrhoea, increased salivation)
- Skin (e.g. rash, sweating, hives, itching, epidermal necrolysis (severe blistering/peeling of the skin), this is extremely rare).

- Nervous System (e.g. agitation, anxiety, dizziness, drowsiness, fits or seizures, paraesthesia (pins and needles))
- Senses – tinnitus, ear pain, eye irritation/pain, increased tearing, visual changes (eg. blurring, double vision), altered taste
- Allergic reaction – if this occurs, it is generally of a mild nature with signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body); rarely of a severe nature, e.g. anaphylactic shock* (sudden onset of signs of allergy described previously in association with low blood pressure, rapid pulse and loss of consciousness)
- Nephrogenic systemic fibrosis - extremely rare condition causing hardening or fibrosis of multiple organs (skin, joints, eyes, internal organs). It is related to exposure to MRI contrast in patients with severe kidney failure.

Other side effects not listed above may occur in some patients. Tell your doctor if you notice anything that is making you feel unwell.

Possible risks from the MRI scan

- The powerful magnetic field of the MRI system will attract iron-containing (magnetic) objects and may cause them to move suddenly and with great force. This can pose a possible risk to the patient or anyone in an object's "flight path." It is essential that you remove all metallic belongings before the MRI scan, including watches, jewellery, and items of clothing that have metallic threads or fasteners. Your doctor may also ask whether you have had previous surgeries, have any metal objects in your body, or have any medical devices (like a cardiac pacemaker) surgically implanted in your body.
- Tell your doctor if being in a fairly tight or confined space causes you anxiety or fear. This fear is called claustrophobia. If you have this condition, your doctor might give you medicine to help you relax.
- It may not be safe to undergo an MRI scan during pregnancy. Please consult your doctor if there is a chance you might be pregnant.

Your doctor will discuss these risks further with you before your scan.

Possible risks for having a biopsy taken

There may be some risks associated with having a biopsy if one is needed. In general terms these may include pain, discomfort, bleeding, bruising, swelling, scarring and infection.

It is important to note that if no abnormalities are seen on the MRI scan, then you will not have to have an additional procedure (e.g. biopsy).

6. What are the possible benefits?

We cannot promise that you will receive any benefits from this research. A possible benefit is that the MRI scan performed before your surgery may show something

important in one or other breast. It is not known if these findings have a long-term benefit. The biggest possible benefit of the main PROSPECT study is that it may help with the identification of future breast cancer patients who can safely avoid radiotherapy.

7. Are there alternatives to participating in screening?

Your participation in this screening process is entirely voluntary and you will be given enough time to decide whether or not you wish to participate. You can decide at any time, without giving any reason, that you no longer wish to participate in this process. This decision will not affect your subsequent treatment or relationship with your treating doctor or the hospital staff in any way.

8. Are there any costs to me from my participation in this study?

These tests will be done without any costs to you. Additionally you will not receive any payment for your involvement in the study.

9. What else do I need to know?

What will happen to information about me?

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purposes stated in this document. It will only be disclosed with your permission, except as required by law. We plan to publish the results of this study. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

All information in relation to the study will be stored in strict confidence, as required by law, on computer disk and/or paper file in locked offices in the [enter name of institution]. Once studies have been completed, records will be retained in a locked storage facility for a prolonged period (over 15 years). Only staff involved with the study will have access to the information. Data from your participation in the study and test results will be stored by the Australian coordinating centre, ANZBCTG and may be kept for future research related to breast cancer. Information about you that will be used in this study will not be labelled with your name, address, or other details that can identify you directly. Instead, it will be assigned a code number that only your doctor can connect back to your name. Your doctor and the study researchers will ensure that all information collected is kept private and your confidentiality will be protected at all times. Information about you will only be disclosed with your permission or if required by law.

If at any time you wish to withdraw from the study, you may do so. In that case, we would hope to continue to store the data already collected, and with your agreement, we would like to continue to collect basic information about your health status in the future. If however, you wish to withdraw from the study and do not want data relating to you personally to be stored, then the data already collected about your health will be 'anonymised'. That is, it cannot be linked to you in any way. Any request about your study data should be made in writing to the ANZBCTG Coordinating Centre through your doctor.

Information about you may be obtained from your health records held at this, and other, health services for the purposes of this research.

Your medical record and any information obtained during the study are subject to inspection, for the purpose of verifying study procedures and the data, by the Therapeutic Goods Administration of Australia and authorised representatives of the Sponsor, Australia and New Zealand Breast Cancer Trials Group, this organisation, [enter name of institution], the [enter name of institution HREC] Human Research Ethics Committee or as required by law. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Information about your participation in this research project may be recorded in your health records.

How can I access my information?

In accordance with relevant [Australian/New Zealand] privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

What happens if I am injured as a result of participating in this research project?

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

Is this research project approved?

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of [enter name of institution].

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

10. Screening Consent

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to the [enter name of institution] concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed) ……

Signature Date

Name of witness to participant's signature (printed) ……

Signature Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed) ……

Signature Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

11. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher [enter name of PI] on [enter tel. no].

For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: [enter name of contact person]

Position: [enter position of contact person]

Telephone: [enter telephone no. of contact person]

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is unclear. You will be given a copy of this information sheet and a signed consent form to keep.

Headed with Institution's name or on Institution's Letterhead

Participant Information and Consent Form

Version 2: 1st December 2013

Project Title: ANZ 1002: Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial (PROSPECT)

Institution conducting study: [enter name of institution]

Principal Investigator: [enter name of PI]

Associate Investigators: [enter name of AI's]

This Patient Information Sheet and Consent Form is ten pages long. Please ensure you have all the pages.

1. Introduction

You are invited to take part in this research study. This is because your breast cancer may be localised to one area in the breast and therefore may not need radiotherapy after surgery.

This Participant Information Sheet and Consent Form tells you about the research study. It explains the tests involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor. If English is not your first language and you need an interpreter, one will be provided for you.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in this research study, you will be asked to sign the consent form at the end of this document. By signing the consent form you are telling us that you:

- understand what you have read
- consent to take part in the research study
- consent to have the tests that are described
- consent to the storage of samples of your breast cancer tissue for future research
- consent to the use of your personal and health information as described.

You will be given a signed copy of this Participant Information Sheet and Consent Form to keep.

2. What is the purpose of this research?

Modern breast cancer treatment is very effective, with a large majority of women not having any recurrence of their disease after treatment. Recurrences still may occur, either in the breast (this is called a local recurrence), or elsewhere in the body (this is called a distant recurrence).

After surgery to remove the cancer from the breast – called a 'lumpectomy', a 'partial mastectomy' or a 'wide excision' - most women are advised to have radiotherapy treatment to the rest of the breast to minimise the risk of local recurrence. Radiotherapy works by destroying remaining cancer cells in the breast, using high-energy X-rays. Radiotherapy treatment has been shown to reduce the chance of a local recurrence after surgery.

The need for radiotherapy depends on the risk of local recurrence occurring after surgery alone. Thus if the chance is minimal, there would be no need for radiotherapy. Some studies have shown that radiotherapy treatment may not be necessary for all women whose cancer is only in the breast and has not spread to other parts of their body (known as early breast cancer).

If radiotherapy treatment can be omitted without there being any more than a very small risk of the cancer coming back in the same breast, more women may be able to avoid radiotherapy in the future. This means that these women would avoid 5 weeks of daily radiotherapy and the possible short term side effects e.g. fatigue, skin redness and discomfort. Radiotherapy is also associated with long term side effects such as discomfort in the breast, thickening of breast tissue, very occasionally possible lung problems (pneumonitis and lung scarring), heart problems and a very small risk of radiation-induced cancer.

The purpose of this study is to see whether magnetic resonance imaging (MRI) can be used to select women with early breast cancer for whom radiotherapy is not needed because the risk of a local recurrence is low. We are investigating whether the abnormalities found by MRI are in fact the reason that local recurrence sometimes occurs. Therefore if no abnormalities are found on MRI, radiotherapy may not be required.

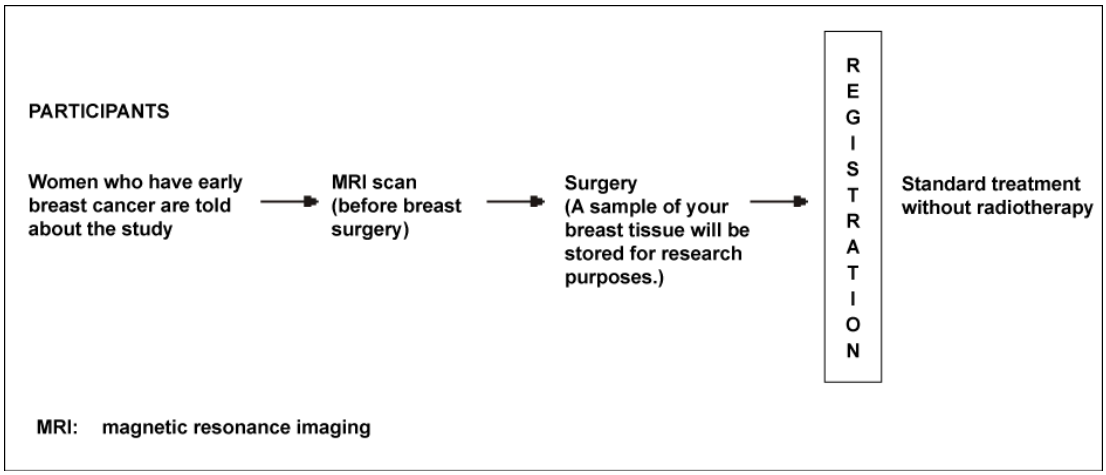
The MRI scan that was done before your breast surgery showed that your breast cancer appeared to be located in just one area of your breast (truly localised). The pathology report of the breast cancer that was removed also showed no unfavourable characteristics, leading us to believe that it is unlikely that you will have a local recurrence. You are therefore being invited to participate in this study, in which you will not receive radiotherapy.

Two hundred women will be invited to take part in the PROSPECT study at selected sites throughout Australia and New Zealand.

This study has been initiated and funded by the Australia and New Zealand Breast Cancer Trials Group (ANZBCTG). The ANZBCTG may be awarded grants to assist in the conduct of this study, from research bodies such as NHMRC or the Cancer Council of Victoria. No member of the research team will obtain any financial benefit from their involvement in this study.

3. What does participation in this research involve?

A summary of what will happen to you during the study is shown in the chart below. Start reading from left to right.



Treatment

While you are taking part in the PROSPECT study you will not receive radiotherapy treatment.

However, you may have endocrine (hormone) treatment, chemotherapy or other treatment. These are all standard treatments for breast cancer and information about these treatment options will be provided to you by your study doctor.

During the study you will return to see your study doctor at the following times after your breast surgery;

- At 3 months and 6 months
- Then, every 6 months until 5 years
- Then, every 12 months until 10 years
- A mammogram will be performed 6 months after your breast surgery and yearly thereafter
- An MRI scan will be performed 18 months after your breast surgery. A blood sample (about 1 tablespoon) will be collected to test your kidney function prior to the scan.

These visits are part of your standard care except the MRI at 18 months.

Expected duration of participation

It is expected that you will participate in this study for 10 years.

4. What will happen to my tumour samples?

By consenting to take part in this study, you consent to the collection, storage and use of your tissue sample collected for future research. Another tissue sample will be collected if breast cancer returns in the same breast.

Your breast tissue samples and any paperwork accompanying the samples will be labeled with a unique study code, not your name or address.

Your blood samples will be tested at the hospital pathology department and will then be destroyed.

i. Tissue banking - primary breast cancer tumour

The researchers will keep a piece of the breast cancer tissue, which was collected at the time of your breast surgery, for future research. If you agree to participate in this study, the tissue sample will be stored in the ANZBCTG Tissue Bank (Newcastle, NSW) for possible future breast cancer research that may or may not be related to the PROSPECT study.

ii. Tissue banking – if breast cancer returns in the same breast

If your breast cancer does return in the same breast (called a local recurrence) the breast cancer tissue will be removed during a surgical procedure. The researchers will keep a sample of this tissue to be stored in the ANZBCTG Tissue Bank. This tissue will be used for possible future breast cancer research that may or may not be related to the PROSPECT study.

This type of testing is done to further our knowledge about breast cancer. The test results will not relate individually to you and will not affect your health or treatment. Therefore you will not be informed of the results of the future research.

5. What are the possible benefits?

We cannot promise or guarantee that you will receive any benefit from participating in this study. Possible benefits may include not needing 5 weeks of daily radiotherapy treatment and therefore avoiding the various potential side effects. Another possible benefit is that if an abnormality is found on the MRI scan performed 18 months after your breast surgery, this will be promptly investigated. The PROSPECT study may help identify women diagnosed with breast cancer in the future who can safely avoid radiotherapy.

6. What are the possible risks?

Possible risk of not having radiotherapy

Every patient has some risk of their cancer returning. Without radiotherapy the chance that your breast cancer may come back in the same breast, called a local recurrence, may be higher than if you had received radiotherapy. If, in the unlikely event that your

breast cancer returns, your study doctor will discuss with you the best available treatment options which will include more breast surgery and possibly radiotherapy.

Possible risks from the dye (contrast) given as part of the MRI scan:

Common side effects (experienced in less than 1 in 20 patients)

- headache
- nausea or vomiting
- local reaction around the injection site, e.g. pain, coldness, warmth, burning sensation

Mostly these are mild and short-lived.

Uncommon side effects (experienced in less than 1 in 100 patients)

- Pain (e.g. chest, back, pelvis, teeth)
- Flu like symptoms (e.g. fever, tiredness, weakness, chest tightness, shivering, generalised feeling of warmth or coldness, throat irritation, running nose, sneezing, shortness of breath or wheezing, cough)
- Gastrointestinal (e.g. abdominal pain, constipation, diarrhoea, increased salivation)
- Skin (e.g. rash, sweating, hives, itching, epidermal necrolysis*(severe blistering/peeling of the skin))
- Nervous System (e.g. agitation, anxiety, dizziness, drowsiness, fits or seizures, paraesthesia (pins and needles)).
- Senses – tinnitus, ear pain, eye irritation/pain, increased tearing, visual changes (eg. blurring, double vision), altered taste.
- Allergic reaction – if this occurs, it is generally of a mild nature with signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, rarely of a severe nature, e.g. anaphylactic shock* (sudden onset of signs of allergy in association with low blood pressure, rapid pulse and loss of consciousness).
- Nephrogenic systemic fibrosis – extremely rare condition causing hardening or fibrosis of multiple organs (skin, joints, eyes, internal organs). It is related to exposure to MRI contrast in patients with severe kidney failure. A blood test will be collected to check that it is safe for you to have the dye used during a MRI scan.

Other side effects not listed above may occur in some patients. Tell your doctor if you notice anything that is making you feel unwell. You will be monitored carefully while you receive the dye during the MRI scan.

Possible risks from the MRI scan:

- The powerful magnetic field of the MR system will attract iron-containing (magnetic) objects and may cause them to move suddenly and with great force. This can pose a possible risk to the patient or anyone in an object's "flight path." It is essential that you remove all metallic belongings before the MRI scan, including watches, jewellery, and items of clothing that have metallic threads or fasteners. Your doctor may also ask whether you have had previous surgeries, have any metal objects in your body, or have any medical devices (like a cardiac pacemaker) surgically implanted in your body.
- Tell your doctor if being in a fairly tight or confined space causes you anxiety or fear. This fear is called claustrophobia. If you have this condition, your doctor might give you medicine to help you relax.
- It may not be safe to undergo an MRI scan during pregnancy. Please consult your doctor if there is a chance you might be pregnant.

Your doctor will discuss these risks further with you before your scan.

The MRI scans may identify other abnormalities in your breasts that may need additional imaging and biopsy.

There may be some risks associated with having a breast biopsy if one is needed. These may include pain, discomfort, bleeding, bruising, swelling scarring and infection. Your doctor will discuss with you the safest way to perform the breast biopsy if you need one.

7. What if new information arises during this research study?

During the PROSPECT study, new information about the risks and benefits of the study may become known to the researchers. If this occurs, you will be told about this new information and your study doctor will discuss whether this new information affects you.

8. Can I have other treatments during this research study?

You can have hormone therapy, chemotherapy and other standard treatments other than radiation therapy for the treatment of your breast cancer.

9. Are there alternatives to participation?

You do not have to participate in this study to receive the medical care you may require. Participation in the PROSPECT study is not your only option. Your other options may include standard breast cancer treatments, including radiotherapy. Your study doctor will discuss these options with you before you decide whether or not to take part in this research study.

10. Do I have to take part in this research study?

Participation in any research study is voluntary. If you do not wish to take part you don’t have to. If you decide to take part and later change your mind, you are free to withdraw from the study at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the [enter name of institution]

11. What if I withdraw from this research study?

If you decide to withdraw from the study, please notify a member of the research team before you withdraw. If you decide to withdraw from the study before it is finished, the researchers will keep and continue to use your information that has already been collected. This is to ensure that the results of the study can be measured properly. However, no further information will be collected. If you do not want this to happen, you should choose not to take part in the study.

12. Could this research study be stopped unexpectedly?

This study will be stopped if an unacceptable number of patients have their breast cancer return to the same breast. If the trial is stopped, you will continue to receive standard breast cancer care and follow up.

13. What will happen when my participation in this research study ends?

Once you have completed the study, your doctor will discuss with you the most appropriate treatment for you at this time.

14. How will I be informed of the results of this research study?

Once the study is complete and the results are known, a written plain English summary of the results of the study will be made available to you upon request. To obtain this please contact one of the investigators listed in section 16.

15. What else do I need to know?

<u>What will happen to information about me?</u>

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purposes stated in this document. It will only be disclosed with your permission, except as required by law. We plan to publish the results of this study. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

All information in relation to the study will be stored in strict confidence, as required by law, on computer disk and/or paper file in locked offices in the [enter name of institution]. Once studies have been completed, records will be retained in a locked storage facility for a prolonged period (over 15 years). Only staff involved with the study will have access to the information. Data from your participation in the study and test results will be stored by the Australian coordinating centre, ANZBCTG and may be kept for future research related to breast cancer. Information about you that will be used in this study will not be labelled with your name, address, or other details that can identify you directly. Instead, it will be assigned a code number that only your doctor can connect back to your name. Your doctor and the study researchers will ensure that all information collected is kept private and your confidentiality will be protected at all

times. Information about you will only be disclosed with your permission or if required by law.

If at any time you wish to withdraw from the study, you may do so. In that case, we would hope to continue to store the data already collected, and with your agreement, we would like to continue to collect basic information about your health status in the future. If however, you wish to withdraw from the study and do not want data relating to you personally to be stored, then the data already collected about your health will be 'anonymised'. That is, it cannot be linked to you in any way. Any request about your study data should be made in writing to the ANZBCTG Coordinating Centre through your doctor.

Information about you will be obtained from your health records, held at the [enter name of institution] and may be obtained from other health services, for the purposes of this researchYour medical record and any information obtained during the study are subject to inspection, for the purpose of verifying study procedures and the data, by the Therapeutic Goods Administration of Australia and authorised representatives of the Sponsor, Australia and New Zealand Breast Cancer Trials Group, this organisation, [enter name of institution], the [enter name of institution HREC] Human Research Ethics Committee or as required by law. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Information about your participation in this research project may be recorded in your health records.

Your local doctor (GP) will be advised of your decision to participate in this research study. By signing the consent section, you agree to your local doctor being notified.

Information about your participation in this research study will be recorded in your hospital medical record.

<u>How can I access my information?</u>

In accordance with relevant [Australian/New Zealand] privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

<u>What happens if I am injured as a result of participating in this research study?</u>

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

<u>Is this research study approved?</u>

The ethical aspects of this research study have been approved by the [enter name of institution HREC]. Human Research Ethics Committee.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (2007), produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Will I be paid for my involvement in this study?

You will not be paid for your participation in this research.

16. Consent

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to the [enter name of institution] concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I consent to the storage and use of my primary breast cancer tissue sample in the ANZBCTG Tissue Bank for future research as described in this document.

I agree that if my primary breast cancer tumour returns, a sample of this tissue can be stored in the ANZBCTG Tissue Bank for future research as described in this document.

I understand that I will be given a signed copy of this document to keep.

Participant's name (printed) ……

Signature Date

Witness (Required when participant cannot read this document for him/herself except where an interpreter is used.)

Name of witness (printed) ……

Signature Date

Interpreter (Required when this document is read to the participant in a language other than English.)

Name of Interpreter (printed) ……

Signature Date

Declaration by Principal or Associate Investigator: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Investigator's name (printed) ……

Signature Date

Note: All parties signing the consent section must date their own signature.

** A senior member of the research team must provide the explanation and provision of information concerning the research project.*

17. Who can I contact?

The person you may need to contact will depend on the nature of your query. Therefore, please note the following:

a. If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in the study (for example, any side effects), you can contact the principal researcher [enter name of PI] on [enter tel. No]

b. If you have any complaints about any aspect of the study, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: [enter name of contact person]

Position: [enter position of contact person]

Telephone: [enter telephone no. of contact person]

APPENDIX B: ECOG Performance Status Criteria

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX C: NCI Common Terminology Criteria for Adverse Events (CTCAE) vs 4.0

Available from the internet at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

APPENDIX D: International Conference on Harmonisation for Good Clinical Practice (ICH-GCP)

Available from the internet at: http://www.ich.org

APPENDIX E: Cancer Australia Guidelines for family history breast cancer risk assessment

To ascertain a patient's risk of breast cancer (due to their family history), an online calculator from Cancer Australia must be used to determine whether the patient has a low, medium or high risk of breast cancer. Gene carriers (BRCA 1,2) or those whose family history of breast cancer reaches the high-risk category of the Cancer Australia risk guidelines are not eligible (refer to Exclusion Criteria 3.2.8).

Please access the calculator using the following link:

https://breastcancerrisk.canceraustralia.gov.au/

Note: as the calculator cannot be used if the patient has already been diagnosed with breast cancer, to determine eligibility for ANZ1002 PROSPECT, answer 'no' to the first question (i.e. Have you ever been diagnosed with breast or ovarian cancer?).

The result of the Cancer Australia risk calculation must be filed in the medical records of all patients participating in ANZ1002 PROSPECT.

APPENDIX F: Bloom Richardson histological scale

Invasive carcinomas of all types should be graded using the Elston and Ellis modification of the Bloom and Richardson grading system. The histological grade is calculated by adding the three scores (tubular differentiation score, mitosis score and nuclear score):

Tumour tubule formation	Score
>75% of tumour cells arranged in tubules	1
>10% and <75%	2
<10%	3

Number of mitoses (low power scanning (X100), find most mitotically tumour area, proceed to high power (x400)	Score
<10 mitoses in 10 high-power fields	1
>10 and <20 mitoses	2
>20 mitoses per 10 high power fields	3

Nuclear pleomorphism (nuclear grade)	Score
Cell nuclei are uniform in size and shape, relatively small, have dispersed chromatin patterns, and are without prominent nucleoli	1
Cell nuclei are somewhat pleomorphic, have nucleoli, and are intermediate size	2
Cell nuclei are relatively large, have prominent nucleoli or multiple nucleoli, coarse chromatin patterns, and vary in size and shape	3

To obtain the final Bloom-Richardson score, add the score from tubule formation plus number of mitoses score, plus score from nuclear pleomorphism. The combined score converts to the following BR grade:

Bloom-Richardson combined scores	Differentiation/BR Grade
3, 4, 5	Well-differentiated (BR low grade)
6, 7	Moderately differentiated (BR intermediate grade)
8, 9	Poorly differentiated (BR high grade)

APPENDIX G: Menopausal status

Pre-menopausal: Estradiol (E2) in the pre-menopausal range (according to institution parameters) prior to pre-registration; the only patients who do not require testing of estradiol (E2) to confirm pre-menopausal status are those patients who have been menstruating regularly during the 6 months prior to registration and have not used any form of hormonal contraception or any other hormonal treatments during the 6 months prior to registration.

Post-menopausal: prior bilateral oophorectomy; aged 60 years or more.

Aged under 60 years:

- with a uterus and amenorrhoea for at least 12 months prior to trial entry
- with a uterus and amenorrhoea for less than 12 months prior to trial entry, FSH level must be in the post-menopausal range
- without a uterus, FSH level must be in the post-menopausal range
- with a uterus and amenorrhoea following endometrial ablation or adjuvant chemotherapy FSH must be in the post-menopausal range

APPENDIX H: Radiology Substudy

Table of Contents

1. Introduction

Magnetic resonance imaging (MRI) of the breast can identify breast pathology that is occult to mammography and ultrasound examination. Currently breast MRI is only funded for surveillance of high risk patients under the age of 50 years. Due to reports of MRI detection of additional foci of synchronous disease in the ipsi- or contralateral [44] breast at the time of diagnosis, it has been included in the algorithm of management of early breast cancer in some international centres and Australian practices, but without clinical trial evidence to support its use.

The presence of additional foci has been well-established by anatomical studies involving serial sectioning of mastectomy specimens and range from 21-63% [36, 37]. Additional foci are often near (2-4 cm) the index cancer. Despite this multifocality and multicentricity, adjuvant whole breast-radiation has provided equivalent survival to mastectomy(22).

The accuracy and impact of MRI on treatment was summarised in a 2008 meta-analysis by Housaami et al [44] Nineteen studies involving 2610 women were included where the MRI- only detection of foci was documented. Additional foci, either multifocal or multicentric were identified in 16% (range 6-34%); 66% were histologically confirmed as malignant. For those who had biopsy-proven additional foci, conversion from wide local excision (WLE) to mastectomy occurred in 8.1% and conversion from WLE to wider or additional excision occurred in 11.3%. In those who did not have histologically-proven additional foci (false positives), the conversion from WLE to mastectomy was 1.1% and from WLE to wider or additional excision was 5.5%. In summary, of every three women with additional lesions detected by MRI only, two will have an additional cancer (true positive) and one will have a false positive. This meta-analysis highlighted that whilst MRI detected additional foci resulted in more extensive surgery, the clinical impact was not clear.

The discovery of additional foci might lead to more extensive surgery with potentially improved local recurrence rates. The UK COMICE study is the only prospective, randomised controlled trial to examine pre-operative breast MRI in early stage breast cancer from 45 centres involving 1623 women [52]. Re-excision rates were the primary objective. Patients with biopsy-proved breast cancer were randomised to MRI or no

further imaging. Re-excision rates were 19% irrespective of MRI use (p=0.77). The overall mastectomy rate was 13% in the MRI group and 8.8% in no MRI group (p=ns).

The PROSPECT study is targeting a different group – namely those over 50 years old with apparently unifocal disease that is of low to moderate risk who may be considered for omission of adjuvant radiotherapy. This group comprises a much larger proportion of the breast cancer population and there is a need to critically assess the performance of breast MRI in this group. We estimate that ~50% of those patients having MRI as part of PROSPECT will not proceed to the formal study due to exclusions found on MRI or at pathology, or due to the patient declining to consent to the study. This substudy aims to use the information from the screening population to investigate the questions of MRI performance.

The number of patients included in this substudy will depend on the number of patients screened to meet the PROSPECT study target accrual (n=200).

2. Objectives

- To determine the frequency of mammographically occult lesions identified on breast MRI at the time of diagnosis in a lower risk group of patients aged ≥50 years
- To determine the type of MRI-only detected lesions
- To determine the impact on surgical management of MRI-only detected lesions
- To assess the correlation between mammographic density, MRI parenchymal volume and background parenchymal enhancement

3. Patient Selection

Patients must meet all pre-MRI entry criteria for the ANZ1002 PROSPECT study. Data for the radiology substudy will be collected from all pre-registered patients.

Patients must have given informed consent using the ANZ1002 PROSPECT screening PICF, which contains information about the radiology substudy. The screening consent must be signed and dated by the patient and the investigator.

4. Study Parameters and Data Management

All patients who meet all pre MRI entry criteria for the ANZ1002 PROSPECT study must sign the ANZ1002 PROSPECT screening consent which includes consent for their data to be collected for the radiology substudy. Patients will be pre-registered as part of the main PROSPECT study (and therefore there is no requirement for a separate registration of patients onto the radiology substudy).

Patients will have a MRI scan and then breast conserving surgery. MRI, surgery and pathology data from all pre-registered patients will be collected for the radiological substudy regardless of the patient's eligibility for the main PROSPECT study

The following data for the radiology substudy will be collected:

Radiology substudy data to be collected	Time of data collection
Family History, Menopausal status, Mammogram, Ultrasound, Core biopsy	Pre-registration visit
Pre-operative MRI data (e.g. parenchymal enhancement, type of lesion, size of lesion)	Post MRI, pre-surgery
Surgery and primary tumour pathology	Post surgery
Post-operative MRI data (e.g. parenchymal enhancement, type of lesion, size of lesion)	18 months post registration (only for patients who enter the ANZ 1002 PROSPECT study)

5. Statistical Analysis

This study will involve a variety of descriptive statistics regarding the frequency of finding occult lesions on MRI and correlation with demographic, clinical and conventional radiological findings. This will be descriptive and hypothesis generating rather than definitive. It is anticipated that this analysis will be performed after all patients have completed screening and 18 months of follow up.

These will be correlated, if possible with baseline characteristics of the screened patient population.

APPENDIX I: Economic Evaluation Substudy

Table of Contents

1. Introduction

ANZ 1002 PROSPECT is a single arm phase II trial that is testing the hypothesis that the reason for an unacceptable rate of local recurrence in those treated with wide excision alone is due to the presence of synchronous lesions that were not detected through standard breast imaging, and that it is these lesions that the radiotherapy is treating. In early stage breast cancer for patients that do not have any synchronous lesions present, it is hypothesised that radiotherapy may be safely omitted.

Staging MRI at the time of diagnosis has been shown to find additional lesions in around 15% of cases. It is hypothesised that these are the lesions that are responsible for the local recurrences, and therefore women with low risk early stage breast cancer with no additional lesions identified on MRI may be able to safely forego radiotherapy.

Reducing radiotherapy would not only reduce inconvenience and short and longer term morbidity, but it would also save resources. However, this benefit needs be weighed against the costs associated with additional MRI scans and associated extra biopsies.

This proposal will evaluate the cost benefits and Quality Adjusted Life Years (QALY) impacts associated with the ANZ 1002 PROSPECT trial. Developing an early economic model allows the economic impact of the ANZ 1002 PROSPECT hypothesis to be explored. These findings will add an economic dimension to ANZ 1002 PROSPECT and would be important when planning follow-up trials and benefit the healthcare consumer and payer by providing evidence around the potential economic and QALY gains.

2. Objectives

The primary objective is to create a dynamic model for the economic evaluation of ANZ 1002 PROSPECT.

The secondary objectives are to evaluate the impact of ANZ 1002 PROSPECT on costs, life years and QALYs.

3. Patient Selection

Approximately 400 MRI-screened ANZ 1002 PROSPECT patients and a similar number of matched control group women who received standard care. Control group women will be identified via the Royal Melbourne Hospital/The Royal Women's Hospital database

and data extracted for demographics, treatment received, and outcomes. Note that while some cost and QALY endpoints will use the full sample, some latter endpoints (subsequent year monitoring costs) will only use the subsample that have sufficient follow-up data to allow these costs to be estimated and compared.

4. Study Parameters and Data Management

The MRI-screened patient group's investigations and treatments will be compared to the investigations and treatments in a control group of women who were not involved in ANZ 1002 PROSPECT (and therefore did not undergo an MRI), but are matched to the women in ANZ 1002 PROSPECT by age, year of diagnosis and clinicopathological characteristics at diagnosis.

In order to compare the cost effectiveness of performing a pre-surgical MRI to current treatment protocols an economic evaluation will be performed. This model will draw on observational data from a single arm cohort of approximately 400 women who were pre-screened as part of the ANZ 1002 PROSPECT study and who had pre-operative breast MRI at Royal Melbourne Hospital/The Royal Women's Hospital. Approximately 190 of these women will have been treated without radiotherapy as part of the main PROSPECT trial, while the others were ineligible for a variety of reasons and treated off-trial. Additional lesions found in all 400 will have been investigated and treated as judged appropriate by the treating team. A control group of a similar number of patients treated at Royal Melbourne Hospital/The Royal Women's Hospital who did not take part in ANZ 1002 PROSPECT will be identified.

The evaluation will consider the following:

1. Differences in the average cost of care between the two cohorts up until and including initial treatment
2. Differences in the downstream cost implications
3. Differences in the impact of screening MRI vs no screening MRI on life years and quality-adjusted life-years (QALYs), including reduction in treatment-related morbidity.

These are discussed in more detail in the following sections.

Differences in the cost of care between performing pre-surgical MRI versus existing protocols

The cost of MRI-screening will include the additional cost of giving all eligible women MRIs. If additional synchronous lesions are discovered during the MRI, ESBC patients may need additional diagnostic workup, such as imaging and biopsies to confirm whether the lesion is benign or not. The costs will therefore equate to the cost of performing MRIs and additional subsequent imaging and biopsies.

Differences in the downstream cost implications

It is expected that approximately 45% of MRI screened early stage breast cancer patients will forego radiotherapy as part of ANZ 1002 PROSPECT (i.e. low background

parenchymal enhancement, favourable final pathology and no additional lesions detected). However, some early stage breast cancer patients who undergo an MRI will have a synchronous cancer lesion detected. These patients will have surgery to remove the additional lesion and radiotherapy treatment will still be recommended. If the MRI images show moderate or greater Background Parenchymal Enhancement, a synchronous cancer cannot be excluded with certainty and radiotherapy treatment is still recommended.

Pre-surgical MRI where synchronous malignant lesions are detected may also result in more extensive surgery. Given the single arm nature of the trial (i.e. no randomised control group available), women in the trial will be matched to women with similar characteristics treated at Royal Melbourne/Royal Women's Hospital to determine their expected treatments had they not undergone MRI.

Systemic management of early stage breast cancer, and follow-up after local treatment is complete, is expected to be similar in both groups, however, an important consideration for downstream cost implications is the possibility of higher recurrence in one protocol versus the other. One possibility is that the frequency of recurrence in the MRI- screened group may be higher than in the control group i.e. the radiotherapy might have treated some cancers that the MRI did not detect. Another possibility is that the identification of occult lesions at baseline will reduce the incidence of ipsi- and contra-lateral lesions during the follow-up period. We will explore the implications for the cost-effectiveness of different levels of recurrence (this can be updated when outcome data on recurrence becomes available as greater follow-up in the single arm trial occurs).

In addition, in the ANZ 1002 PROSPECT protocol, there is additional monitoring for those who forgo radiotherapy (extra MRI at 18 months postoperatively and potentially MRI-directed biopsies). The extra MRI monitoring if this protocol was rolled out in practice may be lower than the current trial, particularly if rates of recurrence are low (i.e. additional MRI was included in the trial as an additional safety measure rather than as part of planned routine care if ANZ 1002 PROSPECT was implemented in practice). We will include a sensitivity analysis in the model to explore the possibility of additional ongoing monitoring costs of differing levels.

Sourcing costs

Procedure unit costs such as MRI and biopsies will be based on MBS costs or Royal Melbourne Hospital/The Royal Women's Hospital information on costs. Hospital inpatient stay unit costs will be estimated using Australian Refined Diagnosis Related Groups (AR-DRG) and Tier2 codes reported in the Australian Government Department of Health National Public Cost Weight Tables combined with the total average length of stay recorded for each procedure reported in the Royal Melbourne Hospital/The Royal Women's Hospital data. These average costs will then be directly applied to the observed hospital procedures (including adverse events etc.) used in the ANZ 1002 PROSPECT cohort and the matched control group.

Where required, and in particular where the MRI finds additional lesions, direct costs incurred after treatment for out-of-hospital services and prescription medicines that are not recorded in the available data will be estimated by using information from the Lifepool cohort (www.lifepool.org). A paper currently under review by Saxby, Petrie, Mann *et al*. has estimated the costs associated with treating early stage breast cancer using this cohort. Costs are estimated from date of diagnosis up to 5 years after diagnosis and include estimated costs by presented cancer characteristics at diagnosis (e.g. lymph node involvement, tumour size and presence of multiple tumours).

For the lifetime modelling and sensitivity analysis the cost of a non-breast cancer death, breast cancer death, a breast cancer recurrence and longer-term healthcare costs incurred after cessation of breast cancer treatment (e.g. > 5 years after diagnosis), will be sourced from an analysis conducted by Cancer Council NSW who has access to the 45 and Up dataset. This dataset includes information on all healthcare costs incurred (Medicare and hospitalisation costs) for NSW residents diagnosed with breast cancer (see Goldsbury *et al.*, 2018). Petrie and Mann are currently working with Cancer Council NSW to finalise a health economics population simulation model for breast cancer.

Differences in the impact on life years and QALYs

The impact on life years will be estimated based on recurrence rates. We will also estimate the impact on the quality of life of treatment related morbidity by utilising health state utility values reported in literature. Utility values will be reported for the following health states:

- Undergoing an MRI
- Undergoing a biopsy
- Undergoing radiotherapy and recovery from radiotherapy
- Additional treatments related to synchronous cancer lesions
- Recurrence.

Summary of Economic Evaluation Important Considerations

A summary of the evaluation components and the key considerations in the standard practice (matched control) and MRI-screened groups is shown in Table 5.

Table 5 Summary of Economic Evaluation Components and Key Considerations in the Control and MRI-screened Groups

Economic Evaluation Component	**Key Model Parameters**	
	Matched Control Group (standard care)	**MRI-screened Group (some having radiotherapy, some not)**
Additional Implementation costs	• None (standard protocol)	• Cost of MRI • Cost of biopsy (ultrasound-

		MRI- guided or open biopsy)
Downstream cost implications	• Cost of surgeries (including proportions of different surgery types) • Cost and frequency of re-excision • Cost and frequency of radiotherapy • Cost and frequency of recurrence	• Cost of surgeries (including proportions of different surgery types) • Cost and frequency of re-excision • Cost of additional therapeutic excision of MRI-detected lesions • Cost and frequency of radiotherapy • Cost and frequency of recurrence
QALYs	• Undergoing radiotherapy • Recovery from radiotherapy • Other treatments • Recurrence	• Undergoing an MRI • Undergoing an MRI and a biopsy • Undergoing radiotherapy • Recovery from radiotherapy • Other treatments • Recurrence

Model

A decision analytical model will be developed which includes a decision tree to account for the pathways that individuals can take under both protocols up until treatment. After this, a Markov model will be built to predict future transitions between being actively screened for cancer, being cancer free, experiencing a recurrence and death. Estimated parameters to govern transition probabilities, and the impact on life years, QALYs and costs, will be based on available observational data from the ANZ 1002 PROSPECT cohort, the matched control group, as well as estimates available in the literature. Moreover, this model will allow for all parameters to be adjusted for example to incorporate contemporary data and allow for technological developments. The decision tree framework for the ANZ 1002 PROSPECT protocol is shown in Figures 2 and 3 (see Sections 6.1.1.1and 6.1.3.1).

Sensitivity Analysis - MRI Sensitivity

During MRI screening, some contrast images can depict significant background parenchymal enhancement, which, in turn, make results interpretation difficult.

Therefore, some women may be directed to undergo radiotherapy due to inconclusive MRI results. The extent of Background Enhancement of the MRI images will impact on the cost effectiveness of the new protocol compared to standard practice. Varying the proportion of patients excluded due to background parenchymal enhancement on MRI imaging will therefore need to be explored in a sensitivity analysis as this will impact the implementation and downstream costs as well as the QALYs for ESBC patients.

Quality of life utility weights

In a recent systematic review of utility weights for different health states experienced during breast cancer screening, treatment and recovery, Bromley *et al.* (2019), with supervision by Dennis Petrie and Bruce Mann, found that there was significant heterogeneity in the weights reported. This heterogeneity includes the methodological approach taken and populations surveyed to derive the utility values as well as the reported duration of time individuals spent in the health states. In order to capture this uncertainty, reviewed health state utility values will be varied via one-way and probabilistic sensitivity analyses. This approach has been previously undertaken by Saxby, Petrie and Mann in evaluating the impact of breast cancer screening on treatment-related quality of life in early stage breast cancer patients. This sensitivity analysis will enable us to construct realistic bounds through which to assess the impact of the intervention on QALYs. However, ultimately, as quality of life research in breast cancer is expanding, this model will be dynamic such that utility weights can be adjusted as contemporary values emerge. It is important to note that this limitation is applicable to all current funding decisions made by governments. Thus, although imperfect, this approach enables comparison with currently funded interventions in breast cancer screening, treatment and ongoing management i.e. we will be using utility values similar to those used by the PBAC, MSAC and the Department of Health.

Time horizon

Given that the trial intervention may result in higher or lower recurrence, it is possible that the benefits of this study will be experienced beyond the 10 year time horizon. We will therefore include a sensitivity analysis which will show the expected outcomes (for example, extrapolated recurrence rates and overall survival) modelled over the cohort's lifetime.

Transition probabilities

In order to capture uncertainty in the transition probabilities and therefore the expected costs in the different treatment arms, a probabilistic sensitivity analysis will be performed. For example, we will explore the implications of varying recurrence rates in the cohorts. This analysis will become more robust as the follow-up of the ANZ 1002 PROSPECT cohort matures.

5. Statistical Analysis

Costs and event related Quality Adjusted Life Years (QALYs) will be compared between the MRI screened ANZ 1002 PROSPECT group and the matched control group. Cost and QALY outcomes will be combined as per standard practice to estimate the cost per QALY and estimate the cost effectiveness of ANZ 1002 PROSPECT relative to standard care.

APPENDIX J: Pre-Registered Patients Outcome Analysis

Table of Contents

1. Introduction

The primary and secondary endpoints of PROSPECT are focused on the cohort of patients found to have unifocal cancer on MRI and low risk pathology, therefore treated without radiotherapy. There are an additional 242 patients who agreed to have MRI but were not found to be eligible to omit radiotherapy according to the protocol. The information from these patients' screening MRI has been used in directing their care. If the primary analysis of PROSPECT shows a sufficiently low risk of local recurrence without radiotherapy in this select group, it will argue that patients with early apparently unifocal breast cancer should undergo MRI with view to selective use of radiotherapy. The impact of MRI on those within the cohort who turn out to be unsuitable for selective radiotherapy will be an important aspect of the consideration as to whether to undergo preoperative MRI.

Collecting follow up data on these patients will help document the full impact of the MRI before initial surgery. Data collection will be similar to the main study: details of surgery and adjuvant therapy; follow up details including dates and timing of imaging; and details of any breast cancer events. The intent is to determine the status of all patients at the scheduled times of initial and subsequent analyses of the main study and as defined by the protocol – namely May 2021 (when the 100th patient has reached 5 years of follow up) and May 2026 (when the 100th patient has reached 10 years of follow up).

We propose to contact the 242 patients who agreed to have MRI but were not found to be eligible to omit radiotherapy to ask them to consent to follow up in order to determine their outcomes and to allow assessment of the overall impact of the 'PROSPECT model of care': MRI for all and selective use of radiotherapy.

2. Objectives

- To determine the outcomes for patients who had MRI but were found to be ineligible for the main PROSPECT study.
- To assess the overall impact of MRI and selective use of radiotherapy across the entire group of patients screened for PROSPECT.

3. Patient Selection

Patients who have had MRI and subsequently been deemed ineligible for the main study will be asked to consent for further research on descriptive analysis. Verbal consent will be accepted from patients who are unable to complete written consent. The consent discussion will be documented in the medical record and on the consent form.

Those patients who refuse to complete the consent and decline participation outright, will not have additional information included, beyond the details collected as part of the screening aspect of the study to which they have already consented. They will be reported as 'refused consent' for all other additional information.

A request to waive consent will be submitted to HREC for those patients who have died in the intervening time, those who are unable to provide informed consent due to mental deterioration and for those who are unable to be contacted. For these patients, information available within the medical records will be used in the study.

4. Study Parameters and Data Management

The following information will be collected for up to 10 years from pre-registration:

- Treatment as per main study patients, but will also include radiation therapy treatment
- Endocrine therapy
- Recurrence; collect on-going data (as per current patients).

Data submission will occur in time for the primary and secondary analyses (see Section 11):

- At primary analysis: Data will be collated and submitted once in preparation for the primary analysis and will include all required data from the intervening period of pre-registration up to and including the primary analysis data cut off.
- At any secondary analysis: Data will be collated and submitted once in preparation for any subsequent secondary analysis and will include all required data from the intervening period from last data submission up to and including the secondary analysis data cut off.

5. Statistical Analysis

Descriptive analysis of the outcomes of the patients in this substudy will be analysed as per Section 11. This will be a separate analysis from the main PROSPECT cohort.

APPENDIX K: PROSPECT Sequencing Substudy

Table of Contents

1. Introduction

The Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial (PROSPECT) clinical trial has used breast MRI in combination with pathological features, to prospectively identify women who might safely avoid radiotherapy due to a low risk of local recurrence.

The study has screened 443 patients over approximately 8 years of recruitment and allocated 201 patients to the no-radiation ("main study") arm. After a median follow up of 60 months (range: 24-120), primary analysis of the 201 patients has revealed a 1% rate of ipsilateral local recurrence, with a total of 3 ipsilateral events observed at 4.5, 6.5 and 7.5 years. In addition, there was one regional recurrence and one regional/distant recurrence. The latter recurrence exhibited a different tumour morphology (lobular phenotype) compared to the index cancer (which had a ductal phenotype). There have been a similar number of contralateral events. For the subset of screened patients who were excluded from the main study (and therefore received radiotherapy), so far there have been 3 ipsilateral events in approximately 230 patients.

These findings – a similar ipsilateral and the contralateral event rate, late local recurrence, and discordant morphology between the distant recurrence and the index lesion – suggest that some of these recurrences could represent independent tumours, rather than true tumour recurrences. This is an important distinction, as adjuvant therapy given at the time of initial treatment is less likely to be effective in reducing the incidence of independent new events.

We propose to conduct sequencing of the index and subsequent lesions to determine whether they are true recurrences or whether they are independent lesions.

We also propose to analyse the index lesion where there has been a subsequent event using the PAM50 assay, to determine whether it may identify those at high risk of recurrence.

2. Objectives

Objective 1.1: Next Generation Sequencing of primary and recurrent tumours to determine whether ipsilateral local or regional and distant events are true recurrences or independent of the primary tumour

Objective 1.2: Exploratory analysis of primary tumour mRNA via PAM50 to determine the nature of the primary that was associated with subsequent events

3. Procedures

To address these questions, we propose to undertake next generation sequencing of the index cancer and matched subsequent events to determine whether these represent true recurrences or whether the metachronous cancers are due to an unrelated second cancer. Germline DNA will also be obtained and sequenced to facilitate the evaluation of the tumours. Tumour mRNA profiling (PAM50) will also be conducted.

All patients have provided consent for use of tissue samples for Ethics-approved research, either as part of consent for the main PROSPECT study or via separate "Tissue Bank Consent". For all future patients in whom there is an eligible event, a request will be made for consent to undertake these analyses in the future.

Samples of the index and matched subsequent lesions and paired blood or buccal samples (where available) will be subjected to DNA/RNA extraction for tumour and germline sequencing, respectively. The samples will be provided to collaborators at the University of Melbourne Centre for Cancer Research (UMCCR) for whole genome and transcriptome sequencing. Bioinformatic analysis will be performed by collaborators at UMCCR and the Walter and Eliza Hall Institute of Medical Research (WEHI) for bioinformatic analysis to determine the relationship between the events.

4. Study Parameters and Data Management

The following results will be collected:

Genomic sequencing and pathology data will be stored indefinitely in secure databases at University of Melbourne or on external cloud-based servers under control of the study investigators. The data obtained from this study may be used for future ethically approved research studies, with prior approval by the principal investigators of this study and HREC.

Study participants' confidentiality and privacy will be maintained. Data including identifying details, minimal clinical history, clinical follow up data and sequencing results will be stored in a password protected database with restricted access. All documents and study data will be stored electronically on the study-specific password-protected database/electronic folders. Only necessary study-related personnel will have password access. All study-related personnel are bound by professional standards of participant information confidentiality and will work to protect participant confidentiality at all times.

5. Outcomes and significance

Findings from this work will directly complement the PROSPECT study. It should reveal the nature of recurrences (*de novo* tumours versus a refractory tumour recurrence).

PAM50 analysis of the index lesion will determine if the PAM50 subtype was unfavourable (e.g. Luminal B) and/or the Risk of Recurrence Score was high. This could have potential utility as an adjunctive test for predicting relapse for patients in this study and therefore could inform future follow up study (or retrospective analysis of additional index tumours).