NCCHTA

09 May 2007

NHS R&D Health Technology Assessment
COMICE Trial

COmparative effectiveness of
MR **I**maging in Breast **C**anc**E**r

Protocol
April 2005
Version 3

University of Hull, and Hull and East Yorkshire NHS Trust

Clinical Trials Research Unit, Leeds

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CHANGES TO PROTOCOL

This version incorporates the following changes from protocol version 2, dated February 2004.

Change	Details
Contacts page	**Trial Co-ordinator, Miss Emma Kalson has now been replaced by Miss Catherine Olivier and Miss Birgit Kindermann** **E-mail addresses and phone numbers updated for Miss Catherine Olivier and Miss Birgit Kindermann**
Page 5	**Exclusion criterion has been amended from** **'have undergone chemotherapy/ hormonal therapy for cancer of the contralateral breast (or other sites) in the previous 12 months'** **to read** **'have undergone chemotherapy/ hormonal therapy for cancer of the contralateral breast (or other sites) in the previous 12 months or have chemotherapy planned to any site before their breast surgery.'**
Page 6, 8, 16, 19	**"…12 months post-randomisation " changed to "…12 months post-radiotherapy "**
Page 40	**GP letter version 2 replaced with version 3 – updated to include new contact details**

CHANGES TO PROTOCOL

This version incorporates the following changes from protocol version 1, dated June 2001.

Change	Details
All references	**NYCTRU changed to CTRU** **Northern and Yorkshire Clinical Trials and Research Unit changed to Clinical Trials Research Unit** **BI-RADS changed to BIRADS** **Telephone contact details for Trials Unit staff and randomisation have changed from 0113 233 XXXX to 0113 343 XXXX** **The WCTN are no longer acting as the Welsh Co-ordinating Centre for the trial**
Contacts page	**Dr Ian Harvey has replaced Stephen Barker as project Manager** **Trial Co-ordinator, Miss Julie Kitcheman has been replaced by Miss Emma Kalson** **Mr Andrea Manca has been added to the Health Economics contacts** **E-mail addresses and phone numbers updated for Professor Lindsay Turnbull, Dr Ian Harvey, Mrs Julia Brown, Miss Jayne Fountain, Miss Vicky Napp and Miss Emma Kalson**
Page 4	**Secondary objectives v) term 'inappropriate mastectomy' changed to 'inappropriate more extensive surgery'**
Page 6	**"…12 months post-radiotherapy" changed to "…12 months post randomisation"**
Page 8	**1.5T changed to high field (1T or 1.5T)**
Page 9	**Section 6. Specific centres removed.** **1.5T changed to high field (1T or 1.5T)**

Page 10	**Randomisation number changed from 0113 233 4925 to 0113 343 4925**
Page 11	**Question GE3 removed from FACT-B** **7.2 Timing of QOL** **HADS, FACT B, Ad-hoc and EQ5D questionnaires will be sent at 8 weeks post randomisation (not at 4 weeks post initial surgery and 4 weeks post repeat operation/ mastectomy)**
Page 14	**Means of collection of Histopathology data has been amended to reduce the size of the CRF and make use of data collection already in place.**
Page 16	**9.2.5 'inappropriate mastectomy' changed to 'inappropriate more extensive surgery', definition altered accordingly**
Page 17	**10.2 accrual updated**
Page 20	**'inappropriate mastectomy' changed to 'inappropriate more extensive surgery'**
Page 23	**WCTN removed.** **Section 15 - Confidentiality statement made more explicit**
Page 31	**Patient information sheet version 1 replaced with version 2 - Confidentiality statements made more explicit and name changed to CTRU**
Page 35	**Consent form version 1 replaced with updated consent form version 3 - Confidentiality clause added and name changed to CTRU**
Page 37	**Consent form 2 version 1 replaced with version 2 – name changed to CTRU**
Page 38	**Investigator Terms of Reference inserted**
Page 40	**GP letter version 1 replaced with version 2 – updated to include new contact details**

CONTENTS

1. BACKGROUND

Currently 14.2% of 50 to 65 year old women with a C5/B5 pre-operative diagnosis undergo more than one operation for primary breast cancer, although the quality assurance standard for the NHS Breast Screening Programme (BASO Specialist Group Meeting, 2000) is < 10% re-operation rate for incomplete tumour excision. Previous studies of surgical treatment for primary breast cancer, without subsequent radiotherapy, have demonstrated an increased risk of local tumour recurrence of 25 to 40% (Leopold et al, 1989; Kurtz et al, 1990), when the initial disease is multi-focal or multi-centric, compared with an 11% recurrence rate when the initial tumour is uni-focal. A higher rate of inadequate/ indeterminate resection margins in specimens with multiple malignant foci may account for these findings, but it has also been shown by detailed sectioning of mastectomy specimens that additional tumour foci are present in 30 to 63% of women mammographically suspected of having uni-focal disease. However, when tumour resection margins are clear and radiotherapy administered, similar rates of recurrence are seen in both uni-focal and multi-focal tumour groups (Hartsell et al, 1994; Kurtz, 1996). Therefore a patient's best chance of successful breast conservation appears to depend on accurate preoperative identification and operative management of all local tumour foci.

Malignant lesions are more difficult to detect in the mammographically dense breast because of technical factors including reduced image contrast and unsharpness and the similarity in density between cancer and normal fibroglandular elements. Contrast-enhanced magnetic resonance imaging (MRI) detects neovascularisation induced by malignant lesions and has already been used to good effect to determine the therapeutic approach.

There is now substantial evidence of a good correlation between the findings at MR imaging and histology of resected specimens, with results exceeding those obtained by X-ray mammography or ultrasound (Davies et al, 1996; Balen et al, 1997; Esserman et al, 1999). In 1993 Harmes et al, using a RODEO technique, demonstrated a good correlation between MR findings and histopathology of lesion margins in lumpectomy patients (Harmes et al, 1993). This work was confirmed three years later by Davies et al, who used a 3D fast spoilt gradient echo, contrast-enhanced, fat-suppressed sequence, and demonstrated an excellent correlation between the largest cancer diameter measured by MR and histopathology, compared with poorer correlation coefficients and larger standard errors for X-ray mammography and ultrasound (Davies et al, 1996). Ando and colleagues presented similar data recently which demonstrated a good correlation between histopathology and direct invasion of mammary tissue, satellite nodule formation and intraductal tumour extension (Ando et al, 1997). Current evidence suggests that chest wall invasion can be diagnosed with confidence, and reports from as early as 1986 quote alteration in patient management following MR, secondary to improved loco-regional staging (Deutch et al, 1993; Whitney et al, 1993; Fischer et al, 1994).

Limited reports of the role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in the clinical management of patients scheduled for breast conservation surgery are available. Tan et al examined 83 patients scheduled for breast conservation therapy and found management to be definitively altered in 18%, with 13% of women undergoing additional surgery (Tan et al, 1999). However, this group was unable to detect factors predictive of alteration in outcome from either patient or tumour characteristics, mammographic results or the timing of MR imaging. In a further larger study in 1999 (463 women with 548 cancers), management was changed in 14.3% of women due to detection of more extensive or multi-centric disease (Fischer et al, 1999). Of the 54 patients

with multi-focal/ multi-centric disease, 48% had breast imaging reporting and data systems (BIRADS) overall breast composition pattern 4, and 52% pattern 3, but no mammographic or ultrasound criterion for defining special subgroups of women with multi-focal or multi-centric disease seen by MR alone were detected.

It is essential that care be exercised in the diagnosis of multi-focal disease, as a preliminary report by Balen et al commented on inappropriate mastectomy in up to 28% of patients (Balen et al, 1997). In a further report by Krämer et al, multiple 3D MR acquisitions obtained at 90-second intervals demonstrated improved sensitivity at 89% compared to 66% for X-ray mammography and 79% for ultrasound, but 17% of women had an incorrect diagnosis of multi-centric disease (Krämer et al, 1997). Of note, both studies utilised 3D imaging of the breast at between 60-90 seconds intervals following bolus injection of the MR contrast agent dimeglumine gadopentetate (Gd-DTPA) and the reduced temporal resolution may have contributed to the false-positive results.

With the detection of increasingly smaller lesions, the specificity of MR imaging becomes crucial to patient management. Currently two approaches have been used to examine contrast uptake characteristics of breast lesions, namely 2D dynamic imaging which allows relatively rapid data acquisition at a limited number of slice locations and 3D high-resolution imaging, with the penalty of increased acquisition time, but with complete coverage of the breast. In addition although the morphological appearance of the lesion may not be diagnostic, spiculation and rim enhancement are highly suggestive of malignancy, whereas a lobulated lesion with internal septations is suggestive of a fibroadenoma. This study employs a compromise by obtaining 'dynamic' data at 45-second intervals using multiple thin slices, which provide full coverage of both breasts, followed by post-contrast, fat-suppressed, high-resolution imaging for morphological information.

The methods of analysis of DCE-MRI data are numerous but empirical techniques are the simplest, least labour-intensive, and the most widely applied. These techniques are used either alone or in combination, to examine contrast uptake relative to background, at pre-determined time points, which have been shown previously to provide best lesion discrimination (Buckley et al, 1994; Gribbestad et al, 1994; Orel et al, 1995; Hulka et al, 1995; Liney and Turnbull, 1999). However these are subject to some inaccuracies resulting from timing and speed of bolus injection and seldom allow for spurious data points secondary to artefacts. Kuhl et al have recently reported on the classification accuracy of experienced radiologists subjectively assessing signal-intensity time curves (Kuhl et al, 1999). These curves were subdivided into those that demonstrated a straight or curved line (Type Ia and b); those with a sharp bend after the initial up slope with plateau thereafter (Type II); and those in which contrast washout was evident after an initial up slope (Type III). Using these criteria the diagnostic efficacy was 86%, with a sensitivity of 91% and a specificity of 83% respectively. This is similar to an earlier report by Knowles et al, who quoted an accuracy rate of 76% for an experienced radiologist using signal intensity time curves alone to differentiate benign from malignant lesions (Knowles et al, 1998). The accuracy value rose to 91% with the addition of morphological information from post-contrast, fat-suppressed images. As a consequence, lesion categorisation in this study relies on both signal intensity time curve evaluation and morphological information (Kuhl et al, 1999).

Controversy exists over the clinical importance of multi-centric foci. Results from correlative radio-pathological studies vary substantially with between 10 to 50% of multi-centric foci reported to be present outwith the index quadrant of the breast (Holland et al, 1985; Vaidya et al, 1996). However most authors agree that more than 90% of early recurrences occur in the index quadrant

whether or not radiotherapy is given (Fisher et al, 1992). As a consequence of these findings some authors argue that small multi-centric foci may not become clinically apparent during a woman's lifetime and that their removal is not necessary (Douek et al, 1998). Indeed others suggest that multi-centric foci may differ from residual tumour in biological potential and hence clinical progression (Sacchini, 1997). However at present the clinical impact of MR-detected multi-centric foci is not known and few surgeons, let alone patients, would condone the deliberate failure to remove all viable cancer in early stage disease to elucidate natural history. This study has reached something of a compromise by choosing to ignore MR-only detected, less than 5 mm in diameter lesions, for which current MR techniques are seldom diagnostic, but biopsying larger lesions prior to definitive surgery.

The cost-effectiveness of MR imaging in this clinical setting is unknown and can only be answered by a randomised controlled clinical trial, which addresses the issues of relative accuracy rates for depicting tumour margins; the uncertainty surrounding pre-operative identification of multi-centric disease, determination of the risk factors for referral for MR imaging; the impact of MR imaging on clinical management, on quality of life and patient satisfaction; and the medium-term ipsilateral breast tumour recurrence rate. Such information will inform those responsible for provision of future health care requirements.

1.1 RATIONALE FOR STUDY DESIGN

The design of this study has been influenced by a number of considerations:

i) Use of technology which is commonly available in a district general setting.
ii) Acquisition of data which can be analysed rapidly without specialist physicist input.
iii) The suggestion by the NHS Health Technology Assessment group for clinical trials to be designed pragmatically, and for multi-centre trials to involve a relatively small number of centres.
iv) The requirement to provide answers quickly to a technology-driven modification of current surgical practice.
v) Use of current NHS Breast Screening Programme quality assurance criteria to minimise additional work-load.

2. AIMS AND OBJECTIVES

The overall aim of this randomised controlled trial is to determine the potential benefits to the patient and to the NHS of the addition of MR imaging to the routine techniques employed for loco-regional staging of primary breast cancer.

The **primary objective** of the study will be to evaluate the role of MR imaging with respect to:

i) Comparison of the repeat operation or mastectomy rates following primary excision between those planned by conventional triple assessment (clinical examination, X-ray mammography and fine needle aspiration cytology/ core biopsy) and those planned by a combination of triple assessment and dynamic contrast-enhanced MR imaging (DCE-MRI). This will include an economic evaluation from a societal perspective of the cost-effectiveness between the two arms.

The **secondary objectives** of the study will include:

i) Determination of the ipsilateral breast tumour recurrence rate for both groups up to five years post-diagnosis.

ii) Comparison of subsequent chemotherapy/ radiotherapy interventions between women planned by triple assessment and those planned by triple assessment and MR imaging combined.

iii) An assessment of the quality of life and patient satisfaction with management decisions based on either triple assessment or triple assessment combined with MR imaging.

iv) An investigation of the risk factors for referral for MR imaging. This will be determined by modelling the different and/or combined approaches to the loco-regional staging of primary breast cancer. This will involve multiple regression analysis of baseline information, including demographic data, history of exogenous hormone consumption and concurrent breast disease, data derived from X-ray mammography, ultrasound and MR imaging, and the cytology and histopathology findings.

v) Evaluation and comparison of the accuracy of loco-regional staging by X-ray mammography, ultrasound and MR imaging, with reference to the tumour extent determined by histopathology of the resected specimens, in particular with respect to more extensive surgery.

vi) Observation of the percentage of patients in whom a change in clinical management occurs after MR imaging.

vii) Follow-up of MR-only detected lesions. This will include identification of the false positive mastectomy rate 12 months post-radiotherapy to allow resolution of radiotherapy-induced changes. Only those patients with lesions which were < 5 mm in diameter at diagnosis and not subjected to biopsy, or those with lesions ≥ 5 mm in diameter but which were negative on biopsy, will be re-evaluated.

3. STUDY DESIGN

This is a multi-centre, randomised, controlled, open, fixed sample, parallel group trial with equal randomisation, in women with biopsy-proven primary breast cancer who are scheduled for wide local excision following triple assessment (clinical examination, X-ray mammography, fine needle aspiration cytology/core biopsy) and breast ultrasound. Patients will be randomised to receive MR imaging or no further investigations. A pragmatic approach to trial design has been chosen so that results will be generalisable in clinical practice and to reduce unnecessary trial costs that are protocol-driven.

The main trial design will also be supplemented with a qualitative study involving a sample of approximately 100 patients, in order to assess patients' subjective and objective experiences of the treatment process and the care pathway.

4. ELIGIBILITY

4.1 INCLUSION CRITERIA

Patients must:

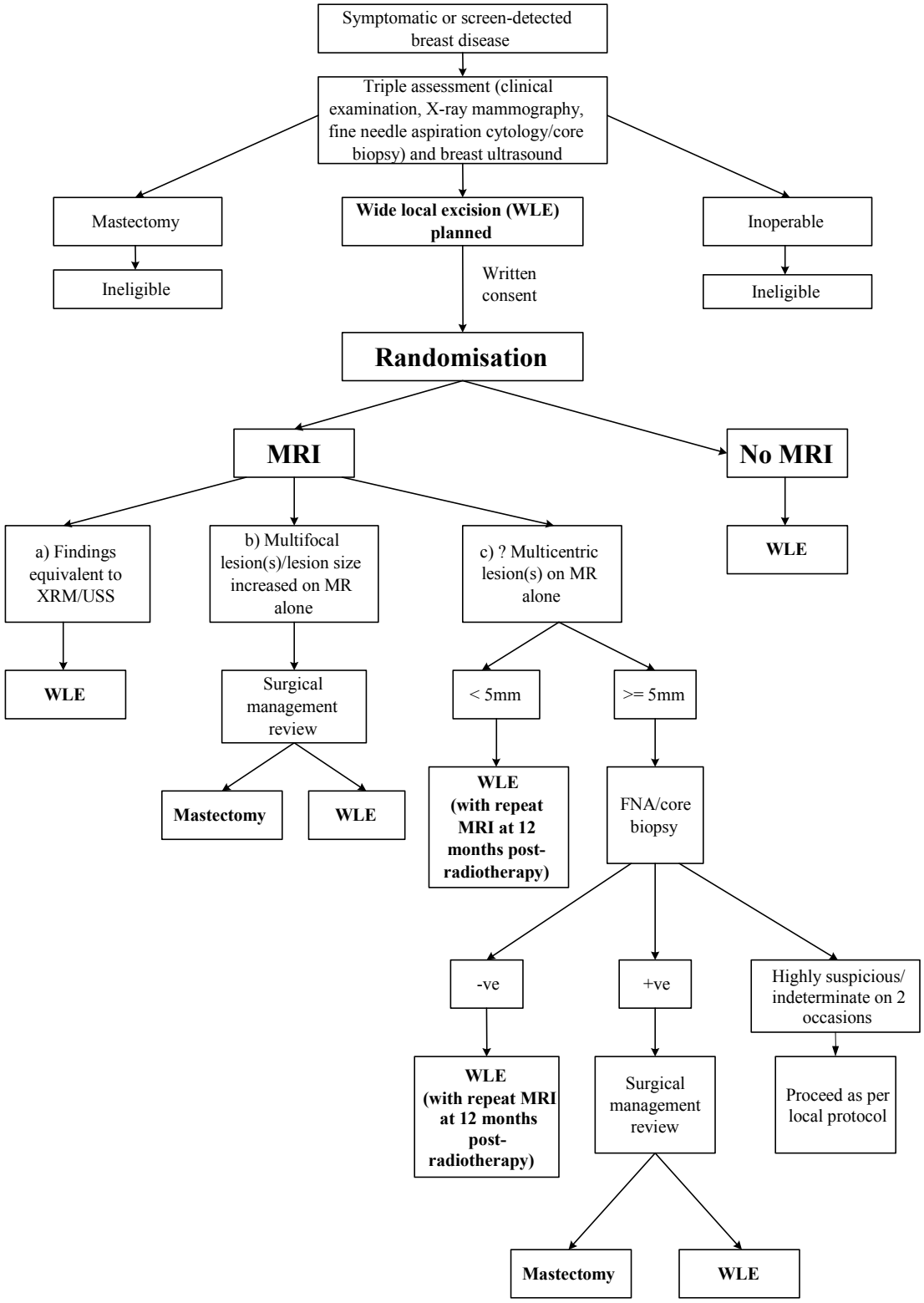
- be aged 18 years or over
- have undergone X-ray mammography *(standard medio-lateral oblique, cranio-caudal and where appropriate paddle/ axillary views carried out within the guidelines of the NHS BSP)*, and ultrasound scanning *(using a 7.5 to 13 MHz linear array transducer)* during the current treatment episode
- have pathologically documented primary breast carcinoma, either from fine needle aspiration cytology or core biopsy
- be scheduled for wide local excision on the basis of existing results
- provide written informed consent.

4.2 EXCLUSION CRITERIA

Patients will be excluded from this study if they:

- are medically unstable
- have a known contraindication to MR scanning
- are known to have had an allergic reaction associated with previous administration of paramagnetic contrast agent or have a severe allergic diathesis
- require renal dialysis
- have undergone chemotherapy/ hormonal therapy for cancer of the contralateral breast (or other sites) in the previous 12 months or have chemotherapy planned to any site before their breast surgery
- have had surgery or radiotherapy for cancer to the ipsilateral breast
- have had surgery to the ipsilateral breast within the previous 4 months for benign breast disease
- have a history of serious breast trauma within the last 3 months
- are pregnant or breast feeding
- have a disability preventing MR scanning in the prone position
- are under the care of a breast surgeon recruiting into the ALMANAC Trial.

5. INVESTIGATIONS AND INTERVENTIONS



5.1 PATIENTS RANDOMISED TO NO MR IMAGING

Patients will receive wide local excision as scheduled. Following wide local excision, patient management and treatment should follow usual practice.

5.2 PATIENTS RANDOMISED TO RECEIVE MR IMAGING

5.2.1 POST RANDOMISATION AND PRE-SURGERY

Women randomised to receive MR imaging should be rapidly assessed so that surgery is not delayed. The MR images should be evaluated by a Consultant Radiologist with prior knowledge of the results of clinical examination, and the results presented to the multi-disciplinary meeting. There are three possible outcomes following review of the mammographic, ultrasound and MR imaging findings:

a) MR imaging findings are equivalent to X-ray mammography and ultrasound: patients should proceed as planned to wide local excision.

b) Multi-focal lesion(s)* are present or the tumour extent is greater than detected on X-ray mammography and/ or ultrasound: surgical management should be reviewed at the multi-disciplinary meeting and the patient should proceed to wide local excision or mastectomy as appropriate. In cases of diagnostic difficulty, MR-localized, ultrasound-guided fine needle aspiration cytology or core biopsy should be considered for confirmation of findings.

** Multi-focal lesions are defined as those located within 2 cms of the index tumour.*

c) Multi-centric* disease is demonstrated by MR imaging: as whole breast coverage during DCE-MRI will require utilization of a 4 mm slice thickness, due to partial volume averaging it is only possible to analyse appropriately lesions of greater diameter than the MR slice thickness. Similarly morphological information from lesions ≤ 4mm in diameter is seldom of clinical utility and reported 'miss' rates for cancer for needle-localised breast biopsy range from 0–7.9% (mean, 2.0%) (Egan et al, 1976; Hermann at al, 1983; Norton et al, 1988; Allen et al, 1994), with some evidence of size dependence (Jackman and Marzoni, 1997). As a consequence a cut-off value of 5 mm has been employed for management purposes as follows:

i) If the multi-centric lesion(s) are **< 5 mm in diameter**, the patient should proceed as planned to wide local excision.

ii) If the multi-centric lesion(s) are **≥ 5 mm in diameter** the patient should undergo MR-localised, ultrasound-guided fine needle aspiration cytology/ core biopsy, or if available locally, MR-guided fine needle aspiration cytology/ core biopsy. If the results are:

- **positive** for malignancy, the surgical management should be reviewed and the patient should proceed to wide local excision or mastectomy as appropriate;

- **negative** for malignancy**,** the patient should proceed as planned to wide local excision;

- **indeterminate,** the patient should undergo repeat sampling. Patients with indeterminate results on two occasions should proceed according to local protocol, but should undergo repeat MR imaging at 12 months as detailed below;

- **suspicious for malignancy** (i.e. C4 or B4) the surgical management should be reviewed and the patient treated as per local protocols.

** Multi-centric lesions are defined as those located in a different quadrant of the breast relative to the index tumour.*

5.2.2 MR IMAGING AT 12 MONTHS

All patients with lesions < 5mm in diameter or ≥ 5mm in diameter and biopsy negative, should undergo repeat DCE-MRI at 12 months post-radiotherapy, to assess persistence of change. Repeat core biopsy/ fine needle aspiration cytology should be carried out for indeterminate/ suspicious enhancing lesions that are ≥ 5mm in diameter.

5.2.3 DETAILS OF MR IMAGING

Dynamic contrast-enhanced MR imaging: All imaging should be performed on a high field (1.5T or 1T) system with a dedicated bilateral breast surface coil for signal reception. Multiple thin slice (in plane resolution 1.3 x 1.3 mm; slice thickness 4 mm) MR sequences (temporal resolution 45 seconds) should be acquired coronally through both breasts out to 450 seconds, the first two data sets obtained prior to, and the remainder following, intravenous bolus injection of contrast agent (0.1 mmol Gd-DTPA/ kg body weight). High resolution (0.7 mm x 0.9 mm in plane) post-contrast, fat-suppressed 3D MR images (allowing maximum intensity projection or multi-planar reformatting) should be obtained coronally for morphological information and further sagittal images acquired if chest wall invasion is suspected. DCE-MRI at 12 months should be performed as detailed above. Data analysis will include:

i) **Evaluation of the behaviour of the signal intensity time curve** should be carried out from the most rapid and strongly enhancing region-of-interest from within any given lesion, taking care to exclude adjacent blood vessels. These areas should be identified semi-automatically by means of parametric images generated by Advantage Windows or equivalent workstations, which selectively mark and allow pixel-by-pixel interrogation of signal intensity change over time on the anatomical images. Lesions should be classified according to morphological appearance and the pattern of the time signal intensity curve as detailed previously (Kaiser and Zeitler, 1989; Fischer et al, 1993; Kuhl et al, 1999). Type I lesions should be considered benign/ normal (score 0); type II – indeterminate (score 1); type 3 – suspicious/ malignant (score 2).

ii) **Morphological criteria of malignancy** will include: ill-defined, irregular or spiculated borders, or peripheral or non-uniform enhancement on high-resolution images. Lesions should be classified as benign/ normal (score 0), indeterminate (score 1) or suspicious/ malignant (score 2).

iii) **Scoring system**: A combined score (time signal intensity curve pattern and morphological information) of 2 or more should be considered suspicious of malignancy, 1 an equivocal

result, and a score of 0 will equal a normal/ benign result. Each lesion demonstrated should be considered independently.

5.2.4 CHANGE IN SURGICAL MANAGEMENT

Changes in surgical management should be obtained by comparing the documented treatment option recorded on a study-specific proforma before randomisation, with those completed after MR imaging.

5.2.5 MR DATA TRANSFER

To facilitate transfer of MR information, the location and extent of tumour tissue should be drawn and separately identified on images of the breast obtained in each orthogonal plane from reformatted images, with reference to the entire breast. The maximum diameter in each plane, the proximity to skin/ chest wall/ nipple retro-areolar complex should be marked on hard copy and sent to both breast surgeon and pathologist. A reference copy should be retained at the MR centre.

6. RANDOMISATION

This is a multi-centre, hospital-based study involving multidisciplinary groups using high field (1T or 1.5T) MR systems (GE, Phillips and Siemens) with dedicated breast coils, fast scanning capabilities and post- processing facilities.

6.1 RECRUITMENT PROCESS

Invitation to participate will be made at the time at which treatment options are discussed and agreed. Whilst at the out-patient clinic, women scheduled for wide local excision will be invited to participate in the study by the Consultant Breast Surgeon or the Consultant Radiologist, but will subsequently receive further information, including the Patient Information Leaflet, from the study research nurse. The research nurse will then contact patients, by telephone, the following working day. If the patient wishes to participate the research nurse will arrange an early (within the next 1-2 working days) and mutually convenient meeting to obtain written consent. Randomisation of consenting patients will be by telephone to the central trials office (the CTRU), using an automated 24-hour telephone randomisation system.

6.2 RANDOMISATION

Randomisation will be administered by telephone by the CTRU, using an automated 24-hour telephone randomisation system. Informed written consent for entry into the study will be obtained prior to randomisation. If the patient is randomised to receive an MRI scan, the scan should be booked and the patient informed of the scan date as soon as possible.

The following information will be required at randomisation:

- basic patient details including name and date of birth
- name of consultant breast surgeon
- confirmation that X-ray mammography and ultrasound have been performed
- mammographic breast density score (1 to 4) evaluated according to the Breast Imaging Reporting and Data System (BIRADS)
- confirmation of eligibility and written informed consent.

Direct line for 24-hour randomisation 0113 343 4925

Once eligibility has been confirmed and the necessary details obtained, patients will be randomised to receive **MR imaging** or **no further investigations** on a 1:1 basis, and will be allocated a trial number. Patient allocation will use a minimisation algorithm, which will employ the following stratification factors:

- **Consultant breast surgeon**

- **Patient's age** subdivided in to
  < 50
  ≥ 50 years of age

- **Breast density***
  a) BIRADS Group 1 (pattern 1 only)
  b) BIRADS Group 2 (pattern 2, 3 and 4).

**Homogeneously or heterogeneously structured dense fibroglandular tissue in a large percentage of the entire breast volume is the only mammographic or ultrasound finding to date which has helped define a subgroup of patients with multi-focal or multi-centric disease detected by MR imaging alone (Fischer et al, 1999; Berg and Gilbreath, 2000). Mammograms will be evaluated according to the Breast Imaging Reporting and Data System (BIRADS) and patients divided in to two groups – Group 1 in which the breast is almost entirely fatty (pattern 1) and Group 2 encompassing those with scattered fibro-glandular densities that could obscure a lesion on mammography (pattern 2); those in whom the breast tissue is of heterogeneous density (pattern 3); and those with extremely dense breast tissue (pattern 4).*

7. QUALITY OF LIFE AND ECONOMIC EVALUATION

7.1 QUALITY OF LIFE ASSESSMENT

In order to evaluate the impact of the investigations and treatment on the quality of life (QOL) of the women involved in the trial, questionnaires will be completed by the patients.

The Functional Assessment of Cancer Therapy, Breast Cancer Version (FACT-B) will be used to evaluate the impact on physical well-being, social well-being, emotional well-being, functional well-being and breast cancer concerns. FACT-B comprises the FACT-General (Cella et al, 1993) and ten

specific items related to breast cancer (Brady et al, 1997). The questionnaire has been developed over a number of years and has been used in several major UK trials (Walker et al, 1999). Satisfactory reliability and validity have also been demonstrated (Cella et al, 1993; Brady et al, 1997). For the purpose of this study the question GE3 "I am losing hope in the fight against my illness" has been removed. This does not affect the scalar structure of the questionnaire.

Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS is a widely used questionnaire which has been shown to be reliable and valid in the detection of clinically significant anxiety and depression in patients with cancer (Razavi et al, 1990; Hopwood et al, 1991; Ibbotson et al, 1994). In addition, HADS scores have been shown to be sensitive to the effects of breast screening and recall within the context of the NHS programme (Walker et al, 1994, Gilbert et al, 1998).

An ad hoc cancer-specific questionnaire using a 4-point Likert scale will be used to examine concerns about tumour recurrence. This questionnaire will be developed and piloted during the first three months of the project. It will address the extent to which patients consider that various aspects of their management have minimised the risk of tumour recurrence. In those undergoing MRI, the perceived impact of this investigation on recurrence and satisfaction with management will be evaluated. The questionnaire will use response formats, such as Likert Scales, that have been shown to have satisfactory reliability and validity in other contexts. It is envisaged that the questionnaire will contain approximately 10 items. During the piloting phase, test-retest reliability will be assessed, and internal consistency (e.g. Cronbach's alpha) will be computed in order to determine if the questionnaire has satisfactory scalar properties. If this is the case, total scores, as opposed to individual items, will be used in the between-group comparisons.

The EQ-5D will be used to measure self-reported utility (EuroQol group, 1990). The EQ-5D is a standardised non-disease-specific instrument which describes and values health-related quality of life and provides a single index value for a number of different health states. The EQ-5D will be used in the economic evaluation (see section 7.3).

7.2 TIMING OF QUALITY OF LIFE ASSESSMENTS AND ADMINISTRATION OF QUESTIONNAIRES

Patients will be asked to complete questionnaires at the following time intervals:

- **HADS** pre-randomisation
  8 weeks post randomisation
  6 and 12 months post initial surgery.

- **FACT-B** pre-randomisation
  8 weeks post randomisation
  6 and 12 months post initial surgery.

- **Ad hoc questionnaire** (to examine concerns about tumour recurrence)
  8 weeks post randomisation
  6 and 12 months post initial surgery.

- **EQ-5D** pre-randomisation
  8 weeks post randomisation
  6 and 12 months post initial surgery.

The first set of questionnaires should be given to the patient after written informed consent has been given, and prior to randomisation. It is essential that the questionnaires are completed by the patient before they are informed of the randomisation allocation, to ensure that all patients complete the questionnaires without any knowledge of any further investigations or treatment changes. The completed questionnaires should be returned to the CTRU. In order to maximise compliance, all subsequent questionnaires will be sent to the patient's home address by the CTRU. The CTRU will endeavour to check the patient's current status with the relevant research nurse before sending questionnaires. Pre-paid envelopes will be provided for the return of questionnaires. Patients not responding within two weeks will be sent a reminder letter. Patients not returning two consecutive sets of questionnaires will not be sent any further questionnaires. A letter of thanks will be sent to patients who return a set of completed questionnaires.

7.3 ECONOMIC EVALUATION

As part of the quality of life questionnaires, a small number of questions will be asked for use in the economic evaluation. These will centre around a woman's time away from usual activities due to her breast cancer treatment, and use of community-based health services.

8. DATA COLLECTION

Data generated by all centres will be collected, monitored and computerised by the NYCTRU. All centres will be asked to complete a log of all patients who are approached to enter the trial including those who refuse randomisation. Data collection for randomised patients will include: initial clinical details pre-randomisation, surgical procedure performed, histopathology, postoperative information, hospital re-admission, and recurrence details as listed below. As some variations in ancillary management (e.g. radiotherapy) and pathological examination exist between centres, the current management policies of each centre will be recorded at baseline and adherence to these policies monitored.

Attempts have been made to reduce data collection to a minimum, with the majority of data being completed by the research nurse and much of the remainder being collected routinely within the framework of the NHS BSP.

8.1 INITIAL CLINICAL DETAILS

The research nurse will collect the following information prior to randomisation:

- patient details (name, date of birth, hospital number)
- height and weight
- menopausal status
- oral contraceptive/ hormone replacement therapy usage
- name of hospital and breast surgeon
- date of diagnosis

- location of tumour at clinical examination
- dates of mammography and ultrasound
- use of pre-operative neo-adjuvant therapy.

8.2 MAMMOGRAPHIC AND ULTRASOUND FINDINGS

The reporting radiologist will record the following information:

- name of radiologist
- background breast pattern on mammography
- location, size and morphological characteristics of all mass lesions, including margin delineation, density, halo and presence of microcalcifications
- presence of stromal deformity, skin changes and pathological nodes
- proximity of tumour to clinically relevant structures
- echo-pattern and presence of acoustic shadowing
- lesion(s) score based on NHS BSP criteria.

8.3 MR IMAGING FINDINGS

The reporting radiologist will record the following data:

- name of radiologist
- location/ maximum diameter of index lesion
- presence, location and maximum diameter of additional multi-focal and or multi-centric lesions
- proximity of the multi-focal/ multi-centric lesions to the index tumour, skin, chest wall and nipple retro-areolar complex
- outcome of MR imaging, i.e. score for each lesion detected
- date/type of additional biopsy or intervention performed.

8.4 CHANGE IN SURGICAL MANAGEMENT

Following MR imaging, the surgical management will be reviewed by the multidisciplinary team. A change to the proposed surgical management will be recorded by the named consultant breast surgeon as either:

- no action
- extended wide local excision
- conversion to mastectomy/quandrantectomy
- conversion to primary chemotherapy.

8.5 SURGERY

The following information will be collected by the surgeon:

- dates of admission/surgery
- type of operation
- intra-operative complications and their management, including fluid replacement, analgesia, antibiotics, need for blood transfusion etc.

- length of time in theatre/anaesthetic time
- other health economics data.

8.6 HISTOPATHOLOGY

Following weighing, serial sectioning of appropriately marked excised specimens (wide local excision or mastectomy) will be carried out with reference to the MR hard copy and in accordance with the guidelines in the NHS BSP publication 'Pathology reporting in breast cancer screening'. These core guidelines contain the 'Minimal dataset for breast cancer histopathology reports' published by the Royal College of Pathologists. A copy of the Histopathology report and the cancer registry form will be collected. The following additional information will be collected by the pathologist:

- size and malignancy of index and additional (multi-focal and / or multi-centric) lesions
- proximity of lesion(s) to skin, chest wall and nipple retro-areolar complex as appropriate
- distance between index and other lesions.
- number of blocks taken

8.7 POST-OPERATIVE INFORMATION

The following information will be recorded by the research nurse for the period from operation to discharge:

- date of discharge
- post-operative complications and their management, including fluid replacement, analgesia, antibiotics, need for blood transfusion etc.
- follow-up arrangements.

8.8 FOLLOW-UP

The following information will be recorded:

At 6 months:
- re-admissions to hospital including reasons and dates
- date and type of further surgery

At 12 months:
- usage of chemotherapy, radiotherapy, adjuvant therapy and entry into other trials
- tumour recurrences (date, site and method of diagnosis)

Up to 5 years:
- tumour recurrences (date, site and method of diagnosis)
- status (date and cause of death if applicable).

9. ENDPOINTS

9.1 PRIMARY ENDPOINTS

9.1.1 REPEAT OPERATION OR MASTECTOMY RATE

The repeat operation or mastectomy (following primary excision) rates will be compared between the two principles under investigation.

9.1.2 ECONOMIC EVALUATION

The economic evaluation from a societal perspective of the two principles under investigation, will include within-trial cost-effectiveness relating differential costs to ipsilateral breast tumour recurrence rate out to 60 months; and an extrapolated cost-effectiveness analysis, where longer term costs and quality-adjusted survival will be modelled on the basis of any difference in trial estimates of recurrence.

9.2 SECONDARY ENDPOINTS

9.2.1 RECURRENCE RATE

Five-year local recurrence rates will be compared.

9.2.2 CHEMOTHERAPY/RADIOTHERAPY INTERVENTIONS

Subsequent chemotherapy/radiotherapy interventions will be compared between women, planned by triple assessment or by triple assessment and MR imaging combined.

9.2.3 QUALITY OF LIFE AND PATIENT SATISFACTION

Quality of life as assessed by the FACT-B, and anxiety and depression as assessed by the HADS, at 8 weeks post randomisation and 6 and 12 months post surgery. Concerns about tumour recurrence post-operatively will be assessed by an ad-hoc questionnaire at 8 weeks post randomisation and 6 and 12 months following surgery.

9.2.4 RISK FACTORS FOR REFERRAL FOR MR IMAGING

The risk factors for referral for MR imaging will be determined by modelling the different and/or combined approaches to the loco-regional staging of primary breast cancer.

9.2.5 EFFECTIVENESS OF IMAGING

Correlation of histopathology results with imaging findings will be performed with particular reference to:

- detection and classification of lesions
- maximum diameter of all foci of invasive/in situ carcinoma present

- anatomical relationship of multi-centric/multi-focal disease to the index lesion and other structures
- location and extent of additional pathologies.

In addition the inappropriate more extensive surgery* rates for combined triple assessment and MR imaging will be examined.

* *Inappropriate more extensive surgery is defined as: pre-operative conversion from wide local excision to more extensive surgery (eg quadrantectomy, mastectomy etc) based on triple assessment plus MR imaging, however subsequent histopathological examination of the resected specimen reveals less extensive breast cancer, which could reasonably have been treated by wide local excision alone.*

9.2.6 CHANGE IN CLINICAL MANAGEMENT

Patients in whom a change in clinical management occurred after MR imaging will be observed.

9.2.7 CLINICAL SIGNIFICANCE OF < 5 MM MR-ONLY DETECTED LESIONS

The clinical significance of < 5 mm diameter lesions not amenable to further pre-operative diagnosis will be ascertained from repeated MR imaging at 12 months post -radiotherapy, and the management changes prompted by their detection documented.

10. STATISTICAL CONSIDERATIONS

10.1 SAMPLE SIZE

Assuming that the addition of MR imaging will reduce overall repeat operation or mastectomy rates following inadequate wide local excision from approximately 15% to 10%, a total of 1840 patients is required, using a chi-squared test without continuity correction, to detect benefit with 90% power at the 5% (2-sided) significance level (Machin et al, 1997).

10.2 ACCRUAL

Accrual at centres will be restricted by scanner, research nurse and radiologist availability. It is anticipated that consent rate of 50% of patient approached will be achievable. We therefore propose to recruit up to 50 centres over the course of the trial that will each recruit approximately 1 patient per week. Randomisation will be equally split to MR imaging or no MR imaging. As the project is funded by the NHS HTA programme, we anticipate that NCRN research will assist in the recruitment process.

11. ANALYSIS PLAN (OUTLINE)

Analysis of the study will be performed in two stages, firstly at completion of the initial follow-up following surgery, and secondly, once the five-year follow-up has been completed in all patients. The primary analysis will be on an intention-to-treat basis. All hypothesis tests will be 2-sided and

at the 5% level: p-values less than 0.05 will be considered to be statistically significant. Formal hypothesis testing will be restricted to the primary endpoints only.

Inference will be based on available data only. Sensitivity analysis will be carried out if there are missing data to test the robustness of the conclusions, the results of which will be fully reported.

11.1 PRIMARY ENDPOINTS

11.1.1 REPEAT OPERATION OR MASTECTOMY RATE

i) The chi-squared test without continuity correction will be used to compare the proportion of patients in the two trial arms who have a repeat operation or mastectomy. 95% confidence intervals will be reported.

ii) A logistic regression model will be fitted, adjusting for the stratification variables and other covariates that are identified as being prognostic of outcome. The adjusted analysis will be reported with the unadjusted analysis.

iii) The impact on the primary endpoint of those patients who choose mastectomy, rather than WLE outside of the definitions for mastectomy within the trial, will be investigated in a sensitivity analysis. In this analysis we will assume that such patients would either all have undergone repeat operation or mastectomy (following initial surgery) or had no further surgery, and investigate how this affects the conclusions in the primary analysis.

iv) Multi-level modelling will be performed to explore whether there is a surgeon effect, and within the MRI arm whether there is a radiologist effect.

11.1.2 HEALTH ECONOMICS ASSESSMENT

The economic evaluation will take the form of a cost-effectiveness analysis and will consist of two parts. The first will be a within-trial comparison of the costs of the two forms of management related to differences in recurrence rates over a five-year period. The second part will involve the use of decision modelling and published data to extrapolate any differences in recurrence rates at five years to longer-term costs and quality-adjusted life expectancy.

WITHIN-TRIAL ANALYSIS

i) Estimating costs. Costs will be estimated from a societal perspective, that is, all costs will be considered no matter on whom they fall. In practice, this is likely to include health service costs (hospital and community-based) and patients' productivity costs. Detailed patient-specific resource use data will be collected after randomisation at the end of the first year of the study. From the health service perspective, these will include details of surgical procedures, key diagnostic procedures, hospitalisations, radiotherapy, chemotherapy, adjuvant therapy, use of primary care and other community-based resources. Details will also be collected of the duration of a woman's stay away from usual activities. Case record forms and questionnaires will be supplemented by detailed assessment of hospital notes in those patients who experience a recurrence over the period of the study. Resource use will be valued in monetary terms using a mixture of published UK unit costs (e.g. British

National Formulary for drug costs (British National Formulary, 2000)) and existing estimates of the unit costs of community-based resources (Netten et al, 1999). Unit costs for hospital resources (e.g. cost per night in a surgical ward, pathology costs, costs per minute in theatre) will be estimated, in collaboration with hospital finance staff, in a sample of trial centres. Productivity costs will be estimated in two alternative ways (Gold et al, 1996): (a) the standard human capital method based on the average UK wage and (b) with adjustment for the extent to which periods away from work are longer than the friction period (i.e. the 'friction cost' method).

ii) Estimating effects. The key measure of effect for the within-trial cost-effectiveness analysis will be recurrence rates over five years. The within-trial analysis will, therefore, relate differential (societal) costs to differential recurrence rates. Within the trial, patients will also be asked to complete the EQ-5D instrument – a preference-based measure of health status - which will facilitate patient-specific health state values over time (Kind, 1996). Whilst the use of the EQ-5D will facilitate a valuable single-index measure of health within the trial, its main use for the economic evaluation will be to provide health state values (utilities) for the extrapolation modelling (see (i) below). The within-trial cost-effectiveness analysis will include discounting of costs and effects (Department of Health, 1995), adjustment for differential follow-up (Lin et al, 1997) and a stochastic analysis using cost-effectiveness acceptability curves (Van Hout et al, 1994).

EXTRAPOLATION MODELLING

The trial is designed to estimate differences in costs and recurrence rates over five years. However, the relative cost-effectiveness of the two forms of management needs an assessment of costs and benefits over a longer time horizon (out-with the feasibility of a trial). Furthermore, the economic importance of any difference in recurrence rates demonstrated in the trial needs to be estimated in terms of longer-term costs and a more general measure of benefit, such as quality-adjusted life years. Decision modelling will be employed for this extrapolation, together with published clinical, economic and epidemiological data (Sonnenberg and Beck, 1993). This work will build upon modelling currently being undertaken at the Centre for Health Economics alongside the ALMANAC Trial. The model would take the form of a long-term Markov model representing disease progression following a loco-regional recurrence. Some data collected in the trial will be important for this modelling, in particular the EQ-5D data which will facilitate estimates of utilities associated with key states in the model. The ultimate objective of the extrapolation modelling would be to estimate differential costs and quality-adjusted life years (QALYs) for both forms of management being assessed in the trial, but over a time horizon of women's lifetimes.

11.2 SECONDARY ENDPOINTS

11.2.1 RECURRENCE RATE

The analysis of time to ipsilateral breast tumour recurrence will be conducted up to five years post completion of radiotherapy (i.e. when there is at least five years follow-up for all patients). Cox's Proportional Hazards Model will be fitted. Adjustment will be made for the stratification variables and other covariates that are identified as being prognostic of outcome. Treatment effects will be

expressed as hazard ratios. Point estimates will be reported with 95% confidence intervals without formal hypothesis testing, as it is anticipated that the trial will have insufficient power to detect differences between the trial arms in recurrence rates.

11.2.2 CHEMOTHERAPY/RADIOTHERAPY INTERVENTIONS

The proportion of women in the two trial arms who have subsequent chemotherapy/ radiotherapy interventions will be compared using a chi-squared test without continuity correction. 95% confidence intervals will be reported. Adjustments will be made for the stratification variables and other covariates that are identified as being prognostic of outcome. The adjusted analysis will be reported with the unadjusted analysis.

11.2.3 QUALITY OF LIFE AND PATIENT SATISFACTION

The six sub-scales of FACT-B (physical well-being, social well-being, emotional well-being, functional well-being, relationship with doctor, breast cancer concerns) and two sub-scale scores for HADS (anxiety, depression) will be transformed to a percentage of the maximum score for each sub-scale. Point estimates and 95% confidence intervals will be reported for the percentage means for each of the sub-scale scores at 6 months. Regression models will be used to adjust for baseline scores and other important covariates. Missing data patterns will be examined carefully. Methods that account for informatively missing data will be used if necessary.

11.2.4 RISK FACTORS FOR REFERRAL FOR MR IMAGING

Risk factors for referral for MRI will be determined by modelling for those patients where mammography and pathology findings do not agree (in terms of tumour presence and extent) whether or not the MRI does agree with the pathology (in terms of tumour presence and extent). This will involve multiple regression analysis of baseline information, including demographic data, history of exogenous hormone consumption and concurrent breast disease, data derived from X-ray mammography, ultrasound and MR imaging, and the cytology and histopathology findings.

11.2.5 EFFECTIVENESS OF IMAGING

Correlation of histopathology results with imaging findings will determine the numbers of true-positive, true-negative, false-positive and false-negative cases for mammography, ultrasound and MR imaging, and hence calculation of sensitivity, specificity, accuracy, positive and negative predictive values will be performed. The percentage of inappropriate more extensive surgery will also be reported for the MRI arm.

11.2.6 CHANGE IN CLINICAL MANAGEMENT

The percentage of patients in whom a change in clinical management occurred after MR imaging will be calculated.

11.2.7 CLINICAL SIGNIFICANCE OF < 5 MM MR-ONLY DETECTED LESIONS

The percentage of clinically significant < 5 mm MR-only detected lesions, ascertained from repeated MR imaging at 12 months post-radiotherapy, will be determined.

11.3 PLANNED SUBGROUP ANALYSIS

For exploratory purposes it is planned to examine the hypothesis that the effectiveness of triple assessment combined with MR imaging compared to triple assessment alone, increases with increasing breast density. This will be tested by fitting interaction terms in the logistic regression models and examining the interactive effects with 95% confidence intervals.

11.4 ADJUSTMENT FOR COVARIATES

Randomisation should result in treatment groups balanced with respect to important prognostic factors or 'covariates'. Adjusting for 'balanced' covariates should result in a reduction in the variance of the treatment effect. Logistic regression will be used to perform the adjustment. With current knowledge, however, it is not possible to specify *a priori* with confidence a list of all the important covariates that will require adjustment. Literature will be reviewed and decisions on the covariates to be used will be made prior to the analysis. The results of any adjusted analysis will be presented alongside the unadjusted analysis, but primacy will be given to the unadjusted analysis for the primary and secondary endpoints.

12. WELL-BEING STUDY

In order to ensure that the views of patients taking part in the trial are fully understood, a sample of participants will be invited to take part in a telephone interview with a trained researcher. The most appropriate methodology for this is the non-schedule standardised interview, as this combines both quantitative and qualitative approaches.

Describing the non-scheduled standard interview (NSSI), Brown and Rutter (1966) state:

'In contrast to most research interviews, the wording and ordering of questions are not rigidly laid down in advance. The idea is rejected that standardisation can be achieved by the use of identically worded questions in the same sequence. Some questions may be given, but the interviewer relies much more on a list of information required. It is his job to inquire into each area … until he is satisfied he has obtained the material. In a certain sense, the schedule may be said to be a questionnaire addressed to the interviewer and not the informant.'

Walker at al have previously developed NSSIs for use in two studies. The first evaluated the lifetime care pathways of pre-school handicapped children who had been referred to a multidisciplinary assessment centre (Walker et al, 1987). The views of referrers, recommenders and parents were sought. The second study used an NSSI to obtain the views of parents about various aspects of their children's behaviour and family relationships (Walker et al, 1984).

The aim of the Well-being Study is to identify patients' subjective and objective experiences of the care pathway, and in particular to identify crisis points, difficulties, strengths and weaknesses to enable subsidiary advice regarding care system re-engineering.

A purposive sample of approximately 100 patients will be selected from the participating centres to reflect the experiences of the whole treatment process.

Women will be invited to participate in a semi-structured taped interview at approximately 12 months post diagnosis. These interviews will seek to obtain detailed information on all aspects of the treatment which have occurred in the 12 months following diagnosis. The interview is likely to last 10-20 minutes and will be recorded on audio-tape for subsequent coding. To maintain anonymity as far as possible recording would only commence after formal introductions have been made and tape boxes would only be identified by study number. Audio-tapes will only be available to COMICE research staff and will be stored in a secure cabinet in the Institute of Rehabilitation at the University of Hull and destroyed on completion of the study.

The interview schedule will be developed and piloted during the first three months of the project and will address key aspects of management as perceived by the patients. In particular, the views of patients regarding the use of MR in their own case will be documented in detail. They will be asked to indicate, in their opinion, which aspects of management were helpful and which aspects were unhelpful. Overall satisfaction with the care received during this period of 12 months will be rated using criteria that will be developed.

The content and response codings will be developed and piloted by the Clinical Psychology Research Fellow during the first three months of the study. A random sample will be selected for independent ratings to assess inter-rater reliability of the codings that will have been developed during the pilot phase. If particular codings prove to be unreliable, these will be altered and a further series of interviews will be rated independently by two raters until satisfactory agreement is achieved.

13. DATA MONITORING

13.1 DATA MONITORING AND ETHICS COMMITTEE

An independent Data Monitoring and Ethics Committee (DMEC) will be established to review the safety and ethics of the trial. Detailed unblinded reports will be prepared by the CTRU for the Data Monitoring and Ethics Committee at 6 and 18 months into the recruitment period. Formal interim analysis will not be conducted, so no adjustment for repeated testing will be necessary in the final analysis.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. An independent chair will be appointed and all grant applicants will be members. The Committee will meet every 6 months.

13.3 DATA MONITORING

Data will be monitored for quality and completeness by the central trials office. At least one attempt will be made to recover data from incomplete forms; reminders will be sent to patients if postal questionnaires are not returned on time. The CTRU will intermittently conduct source data verification exercises on a sample of patients. In addition, the following issues will be monitored: the use of adjuvant treatment and the standard management policy at the various hospitals, the time

from consultation to MR scan and from consultation to surgery, and mastectomy rates due to patient request.

13.4 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues pertaining to all aspect of routine management will be brought to the attention of the DMEC and, where applicable, to individual NHS Trusts.

13.5 QUALITY ASSURANCE STANDARDS

Quality assurance standards are already in place for surgery and X-ray mammography under the auspices of the NHS BSP and these will be adhered to throughout the course of this study. Quality assurance of MR imaging will be undertaken by sending a hard copy of each examination to the CTRU which will be reviewed by experienced MR Radiologists (Professor L W Turnbull and Dr Alan Coulthard) to ensure:

iii) adherence to specified MR imaging protocols
iv) confirmation of reported morphological appearances
v) confirmation of type of signal intensity uptake curve
vi) accuracy of scoring.

Hard copy of all examinations must be retained for 15 years after the completion of the study.

14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, Republic of South Africa, 1996. The study will be submitted to and approved by a Multi-centre Research Ethics Committee (MREC) and the Local Research Ethics Committee (LREC) for each participating centre prior to entering patients into the study. The CTRU will provide the LREC with a copy of the final protocol, patient information sheets and consent forms.

15. CONFIDENTIALITY

The CTRU and collaborative groups will collect patient data that includes some patient identifiers. The latter are required to allow back-identification of patients for the purposes of data clarification and clinical safety monitoring. Patient names will be collected with consent, on one occasion for the purpose of the Quality of Life study. The CTRU and collaborative groups will comply with all aspects of the Data Protection Act 1998. Any information which would allow individual patients or clinicians to be identified will not be released into the public domain.

16. STATEMENT OF INDEMNITY

The COMICE Trial is funded by the NHS Health Technology Assessment programme, therefore HSG(96)48 reference no. 2 applies.

17. STUDY ORGANISATIONAL STRUCTURE

Clinical Trials Research Unit - The CTRU will be responsible for the provision of the randomisation service and for the overall project management, data management, monitoring and statistical analysis of the study.

Centre for Health Economics – The CHE will be responsible for the cost-effectiveness analysis and the design of the relevant case report forms (CRFs).

Trial Steering Committee – The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. An independent chair will be appointed and all applicants will be members. The Committee will meet every 6 months (see Appendix F).

Data Monitoring and Ethics Committee – The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment.

External Project Team - The External Project Team will be responsible for the clinical set-up, on-going management, promotion of the study and for the interpretation of results**.** The team will comprise of a representative from each of the centres involved.

Research Nurses - The research nurses will be responsible for patient recruitment, obtaining consent, randomisation, and co-ordination of all aspects of data collection.

Project Co-ordinator - The Project Co-ordinator will be directly responsible to the Principal Investigator for liaison between: the Project Team, the External Project Team, the CTRU, the Department of Finance at the University of Hull, and the NHS R&D National Co-ordinating Centre for Health Technology Assessment.

Principal Investigator - The Principal Investigator will have overall responsibility for the design, co-ordination and management of the study.

18. PUBLICATION POLICY

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study. Individual participants must not publish data concerning their patients which is directly relevant to the questions posed in the trial until the main results of the trial have been published.

Data will not be released prior to the end of the trial, for study publication or oral presentation purposes, that might either ‘unblind’ the researchers or detrimentally affect the progress of the trial.

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APPENDIX A GLOSSARY OF TERMS

BIRADS	breast imaging reporting and data system
CTRU	Clinical Trials Research Unit
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
FACT-B	Functional Assessment of Cancer Therapy-Breast
FNAC	fine needle aspiration cytology
HADS	Hospital Anxiety and Depression Scale
MRI	magnetic resonance imaging
NHS BSP	National Health Service Breast Screening Programme
QALYs	quality life adjusted years
WLE	wide local excision

APPENDIX B PATIENT INFORMATION SHEET
Version 2, February 2004
(Form to be on headed paper)

COMICE : A study to compare the effectiveness of magnetic resonance imaging (MRI) in breast cancer

INFORMATION SHEET FOR STUDY PARTICIPANTS

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. If anything is not clear or you would like more information, please ask your consultant or one of the members of the team. Thank you for reading this.

What is the purpose of this study?
The usual investigations for women with breast disease are X-ray mammography, ultrasound and fine needle aspiration/ core biopsy. Occasionally these tests may not detect the full extent of disease and some women require a second operation to ensure that all disease is removed. A new breast imaging method is now available: magnetic resonance imaging (MRI). The aim of this study is to see if MRI can provide additional information about the disease compared with X-ray mammography and ultrasound alone, and as a result reduce the number of women requiring a second operation. The full impact of this technique on the women's lives and on the NHS will be assessed.

Why have I been chosen?
You have been invited to take part in this study because you are scheduled to have an operation (a wide local excision) for breast cancer. The study will involve 1840 women from several hospitals in the UK.

Do I have to take part?
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. The standard of care you receive will not be affected if you withdraw from the study at any time, or decide not to take part.

What will happen to me if I agree to take part?
If you decide to take part, you will be randomised either to have an MR scan or to receive no extra investigations. This decision will be made randomly by a computer, i.e. by chance. Half of the women will have no MR scan, half will have an MR scan, and the groups will then be compared. The randomisation will be performed centrally by computer and not by your Breast Surgeon. If you are to have no further investigations, you will proceed as planned to surgery. If you are allocated to have an MRI scan, this will be carried out before your operation. The appointment will be organised so that your planned surgery is not delayed. MR scanning may detect abnormalities that are not detected by X-ray mammography or ultrasound. The results of the scan will be discussed at a multi-disciplinary team meeting. Any suspicious areas identified by the MR scan will be further investigated by needle biopsy. If the results of this are positive, your Consultant Surgeon will discuss this with you. However, it is possible that these abnormalities may subsequently be found to be of no importance, and you will have the operation originally planned.

What does the MR scan involve?
If you are allocated to have an MR scan, both breasts will be examined in addition to the tests that have already been performed. During the scan you will be asked to lie comfortably on your stomach on a special couch, which passes through the MR scanning machine. Throughout the scan you will be able to see out of the machine into the scanning room. You will be able to talk to a radiographer at all times via a two-way intercom system. Before the scan a small needle will be placed in a vein in the back of your hand or in your arm. A dye will be injected through the needle during the MR scan. This is routinely used for this type of examination and causes very few problems, mostly mild allergic type reactions. During the scan you will hear knocking noises as the pictures are taken. The MR scan takes between 30 - 45 minutes. **A relative or friend may come in to the scan room with you.**

What are the side-effects of the MR scan?
Our radiographers will check that you do not have any conditions such as pieces of metal in your body that may cause problems during an MR scan. The dye injected during the scan is associated with very few problems, the most common being slight pain at the site of injection and mild allergic-type reaction, for example skin rash.

What are the possible disadvantages and risks of taking part?
It is possible that the MR scan may show abnormalities that are later found to be of no importance, and as a result you would have undergone unnecessary additional tests (needle biopsy). There is also a small chance that the MR findings will suggest that more extensive surgery should be performed than is actually necessary.

What are the possible benefits of taking part?
Your planned operation is a wide local excision. For some women, the pathology findings from this surgery show that a second operation is required. We hope that the MR scans will provide additional information to show which patients require more extensive surgery before the operation is carried out, to prevent a second operation.

What if something goes wrong?
If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during this study, the normal National Health Service complaints mechanisms should be available to you. Information about patient rights, research-related questions and research-related injury can be obtained from the Local Patients Action Teams or the charity CancerBACUP.

Will the information obtained in the study be confidential?
All information collected about you for this study will be kept strictly confidential. This information will be securely stored at the COMICE Study Offices on paper and electronically under the provision of the 1998 Data Protection Act. Anything you say will be treated in confidence, no names will be mentioned in any report of the study, and care will be taken so that individuals cannot identify you from details in reports from the results of the study. Only appropriately-qualified members of the COMICE research team may confidentially review your medical records. This is to ensure that the study is carried out to the highest possible scientific standards. In order to be able to

check your notes we will need to hold some information, such as your date of birth and hospital number, so that we can identify your notes accordingly.

What other information will be collected in the study?
With your agreement, information will be obtained about any medication you are currently taking, the findings from X-ray mammography and ultrasound, the type of operation carried out, the pathology findings from the tissue removed, and your post-operative recovery. If you agree to take part in the Quality of Life study, you will be asked to fill out 4 short questionnaires at baseline, 8 weeks after randomisation, and 6 months and 12 months after your operation to find out how you feel. Another short questionnaire will be given to you if any further problems develop. In order to send these to you we will need to collect your full name and address. We may also contact you in 12 months time to ask you if you would take part in a more detailed interview about your treatment and how you have been feeling. We would contact you nearer the time and give you a separate information sheet for this part of the study.

Can I withdraw from the study at any time?
You are free to refuse to join the study and may withdraw at any time or choose not to answer certain questions.

Will anyone else be told about my participation in this study?
We will inform your GP that you are helping with this study, unless you ask us not to. Your name will not be disclosed outside of the Study Offices or GP surgery.

What will happen to the results of the study?
The results of this study will be published in a medical journal approximately 12 months after the last patient has been entered. The results will also be available in 2006 on the following web site: http://www.hta.nhsweb.nhs.uk.

Who is organising and funding the research?

This study is being conducted in co-operation with the Clinical Trials Research Unit at the University of Leeds, and the Centre for Health Economics at the University of York. It is funded by the National Health Service Research and Development Programme for Health Technology Assessment.

The study has been approved by the North-West Multi-centre Research Ethics Committee.

Contact for further information
If you have problems or questions, please do not hesitate to get in touch. Please use one of the following contact numbers:

Thank you for considering this study.

APPENDIX C PATIENT CONSENT FORM
Version 3, February 2004

(*Form to be on headed paper)*

Study Number:

PATIENT CONSENT FORM

Title of Project: COMICE Trial - Examining the comparative effectiveness of contrast-enhanced high field MRI in women scheduled for wide local excision

Research Nurse:

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version ……) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the research staff or from regulatory authorities where it is relevant to my taking part in research; I give permission for these individuals to have access to my records. ☐

4. I understand that my medical data will be collected for this study and may be used to help develop new research, and that data protection regulations will be observed and strict confidentiality maintained. ☐

5. I consent to donation of surplus tissue left over from my breast surgery, that is not required for diagnosis and treatment, to be used for laboratory research into breast disease. ☐

6. I consent to the storage, including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐

7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Researcher taking consent	Date	Signature

1 for patient; 1 for CTRU; 1 to be kept with hospital notes

APPENDIX D PATIENT INFORMATION SHEET FOR NON-SCHEDULED INTERVIEWS
Version 1, June 2001

(Form to be on headed paper)

Study Number:

PATIENT INFORMATION SHEET 2

Title of Project: COMICE Well-Being Study

Name of Researcher:

This sheet is an additional information sheet for the COMICE study in which you already participating. In order to obtain information about how ladies feel following their treatment, we are asking a sample of participants to take part in a telephone interview with a trained researcher. If you are willing to take part in this part of the study, a researcher will talk to you about how your diagnosis and treatment has affected your feelings. The researcher will need to talk to you for about 10-20 minutes over the telephone at a time convenient to you. The interview would be recorded on audiotape to allow the interviewer to play back the interview and take accurate notes. The recording would only be available to the research staff and would be destroyed at the end of the study. Your responses would not be fed back or reported in any way that could identify you as an individual.

If you are happy to take part in this part of the study, you will be asked to sign a consent form to show that you understand what is involved. We wish to emphasise that you do not have to take part in this study. If you decide not to participate, your treatment will not be affected in any way.

Contact for further information
If you have problems or questions, please do not hesitate to get in touch. Please use one of the following contact numbers:

_____

_____

_____

Thank you for considering this study.

APPENDIX E PATIENT CONSENT FORM
Version 2, February 2004

(Form to be on headed paper)

Study Number:

PATIENT CONSENT FORM 2

Title of Project: COMICE Well-Being Study

Research Nurse:

1. I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that my information will be recorded on audio-tape for this study and that data protection regulations will be observed and strict confidentiality maintained. ☐

4. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Researcher taking consent	Date	Signature

1 for patient; 1 for CTRU; 1 to be kept with hospital notes

APPENDIX F TRIAL STEERING COMMITTEE TERMS OF REFERENCE

The terms of reference of the Trial Steering Committee are as follows:

1. To provide overall supervision of the trial.

2. To monitor and supervise the progress of the trial towards its overall objectives, adherence to the protocol and patient accrual within the set time frame.

3. To review at regular intervals relevant information from other sources (e.g. other related trials), and recommend appropriate action (e.g. changes to trial protocol, stopping or extending the trial).

4. To recommend appropriate action in light of points 1, 2 and 3, to ensure that the rights, safety and well-being of the trial participants are the most important considerations and prevail over the interests of science and society.

APPENDIX G DATA MONITORING AND ETHICS COMMITTEE TERMS OF REFERENCE

The terms of reference of the Data Monitoring and Ethics Committee are as follows:

1. To determine if additional interim analyses of trial data should be undertaken.

2. To consider the data from interim analyses, unblinded if considered appropriate, plus any additional safety issues for the trial and relevant information from other sources.

3. In the light of 2., and ensuring that ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee and to recommend on the continuation of the trial.

4. To consider any requests for release of interim trial data and to make recommendations to the TSC on the advisability of this.

5. In the event of further funding being required, to provide to the TSC appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study.

APPENDIX H INVESTIGATOR TERMS OF REFERENCE

1. The CTRU will be responsible for the day-to-day management of the study which includes randomisation, data management, data monitoring, data validation and statistical analysis.

2. The investigator agrees to carry out the study in accordance with the most recent MREC-approved study protocol.

3. The study can commence in the investigator's hospital once Local Research Ethics Committee (LREC) approval is given by the relevant local committee. The investigator will keep the CTRU fully informed as to the progress of any such requests for approval to the LREC and will provide a copy of the approval letter once received.

4. The recruitment of patients is to be carried out strictly in accordance with the inclusion and exclusion criteria as defined in the protocol. The investigator is responsible for ensuring that written informed consent is obtained for all patients prior to randomisation into the COMICE trial.

5. The investigator must provide the CTRU with a list of their staff members authorised to sign CTRU-approved case report forms, together with a sample of each authorised signature. The investigator must also ensure that the CTRU are kept informed of all staff changes and provide samples of authorised signatures for all new staff.

6. The investigator must ensure that all data collection forms are completed at the correct times and forwarded to the CTRU within one month of the timing of assessment. If this commitment is not met, the CTRU may not be able to deliver the trial results on time.

7. The investigator must ensure that all data collection forms are only completed by or amended by authorised signatories, that all forms are signed and dated and that all amendments are initialled and dated by authorised signatories.

8. To avoid unnecessary data chasing, the investigator agrees that where data are missing or inaccurate and only where additional supporting evidence exists to complete the missing data or amend inaccuracies, senior CTRU staff may complete data collection forms on behalf of the investigator. The CTRU agrees to only make such amendments where there is no doubt about the validity of an amendment, and to initial and date all amendments. For example, i) where an eligibility question regarding age has not been answered and the Date of Birth and Date of Randomisation are given, senior CTRU staff may answer the question on the basis of calculated age at randomisation. ii) Where a blood sample date has not been entered, but a copy of the laboratory report has been received by the CTRU, CTRU staff may transfer the date to the data collection form, with a note to say where the data came from.

9. Individual investigators must not publish data concerning their patients which is directly relevant to the questions posed in the study until the main results of the study have been published and then only with prior consent from the CTRU.

10. The investigator and the CTRU agree to conduct the study in accordance with the Data Protection Act 1998.

11. The investigator agrees that the local Cancer Registry can be contacted to release data about his/her patients to monitor patient representativeness in the trial.

APPENDIX I GP LETTER

Version 3, April 2005

GP Letter

Notification of patient entry into the COMICE Trial

Dear Dr .....

Patient name .....

The above-named patient from your practice has consented to enter a randomised controlled trial to evaluate the comparative effectiveness of magnetic resonance imaging in women scheduled for a wide local excision following X-ray mammography, ultrasound and needle biopsy for breast cancer (the COMICE Trial). The trial is funded by the NHS Health Technology Assessment Programme, and the Principal Investigator is Professor Lindsay Turnbull from Hull Royal Infirmary.

The patient has been given the information leaflet (a copy of which is attached) and is aware that she can withdraw from the study at any time without giving a reason.

Data collection forms are to be completed by the consultant or a member of his/her team from entry into the study for five years. Follow-up will be organised by the trial team and should not entail any additional workload for you. The women involved in the trial are being asked to complete quality of life questionnaires pre-randomisation, and then eight weeks post randomisation, and six and 12 months post initial surgery, which will be sent to their home address for completion.

If you require any further details about this study, please do not hesitate to contact the Trial Co-ordinators, Catherine Olivier or Birgit Kindermann at:

Clinical Trials Research Unit
17 Springfield Mount
Leeds
LS2 9NG
Tel: 0113 343 1494/1482
Fax: 0113 343 1471

Yours sincerely

.....

On behalf of Mr X, Consultant Breast Surgeon

ACKNOWLEDGEMENTS

The applicant body would like to thank the NHS R&D Health Technology Assessment group for funding, and other colleagues in all specialities who have helped in the development of this study.