Health Technology Assessment 2010; Vol. 14: No. 1

Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE)

LW Turnbull, SR Brown, C Olivier, I Harvey, J Brown, P Drew, A Hanby, A Manca, V Napp, M Sculpher, LG Walker and S Walker, on behalf of the COMICE Trial Group

January 2010
DOI: 10.3310/hta14010

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

How to obtain copies of this and other HTA programme reports
An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

– fax (with **credit card details**)
– post (with **credit card details** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services' (out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of *HTA on DVD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE)

LW Turnbull,[1]* SR Brown,[2] C Olivier,[2] I Harvey,[1] J Brown,[2] P Drew,[3] A Hanby,[4] A Manca,[5] V Napp,[2] M Sculpher,[5] LG Walker[6] and S Walker,[5] on behalf of the COMICE Trial Group

[1]Centre for MR Investigations, University of Hull and Hull and East Yorkshire Hospitals NHS Trust, UK
[2]Clinical Trials Research Unit, University of Leeds, UK
[3]Hull York Medical School, UK
[4]Leeds Teaching Hospitals Trust, Leeds, UK
[5]Centre for Health Economics, University of York, UK
[6]Institute of Rehabilitation and Oncology Health Centres, University of Hull and Hull and East Yorkshire Hospitals NHS Trust, UK

*Corresponding author

Declared competing interest of authors: none

Published January 2010
DOI: 10.3310/hta14010

This report should be referenced as follows:

Turnbull LW, Brown SR, Olivier C, Harvey I, Brown J, Drew P, *et al*. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). *Health Technol Assess* 2010;**14**(1).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 99/27/05. The contractual start date was in June 2001. The draft report began editorial review in October 2008 and was accepted for publication in June 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.

Abstract

Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE)

LW Turnbull,[1]* SR Brown,[2] C Olivier,[2] I Harvey,[1] J Brown,[2] P Drew,[3] A Hanby,[4] A Manca,[5] V Napp,[2] M Sculpher,[5] LG Walker[6] and S Walker,[5] on behalf of the COMICE Trial Group

[1]Centre for MR Investigations, University of Hull and Hull and East Yorkshire Hospitals NHS Trust, UK
[2]Clinical Trials Research Unit, University of Leeds, UK
[3]Hull York Medical School, UK
[4]Leeds Teaching Hospitals Trust, Leeds, UK
[5]Centre for Health Economics, University of York, UK
[6]Institute of Rehabilitation and Oncology Health Centres, University of Hull and Hull and East Yorkshire Hospitals NHS Trust, UK

*Corresponding author

Objectives: To determine whether the addition of magnetic resonance imaging (MRI) to current patient evaluation by triple assessment would aid tumour localisation within the breast and thus reduce the reoperation rate in women with primary breast tumours who are scheduled for wide local excision (WLE), and to assess whether the addition of MRI would be cost-effective for the UK NHS.
Design: A multicentre, randomised controlled, open, parallel group trial with equal randomisation. The main design was supplemented with a qualitative study to assess patients' experiences of the treatment process and care pathway, and involved the development of a non-scheduled standardised interview (NSSI).
Setting: The study took place at 45 hospitals throughout the UK.
Participants: Women aged 18 years or over with biopsy-proven primary breast cancer who had undergone triple assessment, were scheduled for WLE, and were capable of providing written informed consent.
Interventions: Patients were randomised to receive MRI or no MR1. Randomisation was performed using minimisation, incorporating a random element. All MRI was performed at 1.5T or 1.0T with a dedicated bilateral breast coil.
Main outcome measures: The primary end point of the trial was the reoperation rate. Secondary outcome measures included discrepancies between imaging and histopathology, and the effectiveness of using both procedures; change in clinical management after using MRI; the clinical significance of MRI-only-detected lesions; the rate of interventions; the ipsilateral tumour recurrence rate; patient quality of life (QoL); and cost-effectiveness.
Results: From a total of 1623 patients, 816 were randomised to MRI and 807 to no MRI. No differences in reoperation rates were found between the two groups of patients [MRI patients 18.75%, no MRI 19.33%, difference 0.58%, 95% confidence interval (CI) –3.24 to 4.40]. Therefore, the addition of MRI to conventional triple assessment was not found to be statistically significantly associated with a reduced reoperation rate (odds ratio = 0.96, 95% CI 0.75–1.24, $p = 0.7691$). The best agreement between all imaging modalities and histopathology with regard to tumour size and extent of disease was found in patients over 50 years old with ductal tumours NST and who were node negative. In the imaging arm, mastectomy was found to be pathologically avoidable for 16 (27.6%) out of 58 patients who underwent the procedure. There were no significant differences between the groups regarding

the proportion of patients receiving chemotherapy, radiotherapy or additional adjuvant therapies, as well as for local recurrence-free interval rates and QoL. An acceptable NSSI was developed for use in this population of patients. Economic analysis found no difference in outcomes between the two trial arms.
Conclusions: The addition of MRI to triple assessment did not result in a reduction in operation rates, and the use of MRI would thus consume extra resource with few or no benefits in terms of cost-effectiveness or HRQoL. However, MRI showed potential to improve tumour localisation, and preoperative biopsy of MRI-only-detected lesions is likely to minimise the incidence of inappropriate mastectomy.
Trial registration: Current Controlled Trials ISRCTN57474502.

Contents

List of abbreviations

ACR BI-RADS	American College of Radiologists breast imaging reporting and data system
BMI	body mass index
CI	confidence interval
CIS	carcinoma in situ
CRF	case report form
CTRU	Clinical Trials Research Unit
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
DCIS	ductal carcinoma in situ
DMEC	Data Monitoring and Ethics Committee
EQ-5D	EuroQol 5 Dimensions (questionnaire)
ER	estrogen receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast
FNAC	fine needle aspiration cytology
FSPGR	fast spoiled gradient echo
HADS	Hospital Anxiety and Depression Scale
HER2	human epidermal growth factor receptor 2
HRQoL	health-related quality of life
HRT	hormone replacement therapy
ICE	imputation by chained equations
ITT	intention-to-treat
LCIS	lobular carcinoma in situ
LREC	Local Research Ethics Committee
MID	minimally important difference
MREC	Multicentre Research Ethics Committee
MR	magnetic resonance
MRI	magnetic resonance imaging
NHS BSP	National Health Service Breast Screening Programme
NSSI	non-schedule standardised interview
OLS	ordinary least squares
OR	odds ratio
PR	progesterone receptor
RAC	retro-areolar complex
QALY	quality-adjusted life-year
QoL	quality of life
SD	standard deviation
TMG	Trial Management Group
TOI	Trial Outcome Index
TSC	Trial Steering Committee
USS	ultrasound scan
WLE	wide local excision
XRM	X-ray mammography

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

In 2001–2 the reoperation rate for positive margins following wide local excision (WLE) averaged 14.2%, whilst in the most recent audit reported in 2006–7 this value had risen to 17.0%. This reoperation rate constitutes a considerable additional burden both to the patient and the UK NHS. The NHS Breast Screening Programme (NHS BSP) quality assurance target reoperation rate is 10%.

Objectives

The main objective of the COMICE trial was to determine whether the addition of magnetic resonance imaging (MRI) of the breast to current patient evaluation by triple assessment (clinical, radiological and pathological) would aid tumour localisation within the breast and hence reduce the reoperation rate in women with primary tumours who were scheduled for WLE. The cost-effectiveness of MRI in this clinical setting was unknown and the economic analysis of this trial attempted to answer the question whether the addition of MRI was worthwhile from the perspective of the NHS.

Methods

Design

COMICE was a multicentre, randomised, controlled, open, parallel group trial with equal randomisation in women with biopsy-proven primary breast cancer who were scheduled for WLE following triple assessment. Patients were randomised to receive MRI or no MRI. A pragmatic approach to trial design was chosen so that results could be generalisable in clinical practice and to reduce unnecessary protocol-driven trial costs.

The main trial design was also supplemented with a qualitative study of 100 patients, in order to assess patients' experiences of the treatment process and the care pathway. This supplemental study included the development and validation of a non-scheduled standardised interview (NSSI) to assess the self-reported psychosocial effects of specific aspects of trial participation.

Setting

This study took place at 45 hospitals throughout the UK.

Participants

Women aged 18 years or over, who had undergone X-ray mammography and ultrasound scanning (USS) during the current episode, had pathologically documented primary breast carcinoma, and were scheduled for WLE and capable of providing written informed consent, were recruited. Patients were excluded if they were medically unstable, had a known contraindication to MR scanning or use of a paramagnetic contrast agent, had renal failure, had undergone chemotherapy/hormonal therapy in the previous 12 months or had undergone previous surgery, radiotherapy or serious trauma to the ipsilateral breast, were pregnant or breastfeeding, or had a disability preventing prone scanning.

Interventions

Patients were randomised to receive MRI or no MRI. Randomisation was performed using minimisation incorporating a random element. The following minimisation factors were incorporated: consultant breast surgeon, patient's age (< 50 years versus ≥ 50 years) and breast density [American College of Radiologists breast imaging reporting and data system (ACR BI-RADS) pattern 1 versus ACR BI-RADS pattern 2, 3 or 4].

All MRI was performed at 1.5 T or 1 T with a dedicated bilateral breast coil. Dynamic contrast-enhanced MRI utilised a T1-weighted, three-dimensional fast spoiled gradient echo (FSPGR) sequence (temporal resolution 45 seconds), acquired following intravenous injection of contrast agent (0.1 mmol Gd-DTPA/kg body weight), and high-resolution (0.7 mm × 0.9 mm in plane) fat-suppressed T1-weighted three-dimensional SPGR images were acquired for lesion morphology. Data

analysis included evaluation of the signal–intensity time curves and lesion morphology.

Main outcome measures

The primary end point of the COMICE trial was the reoperation rate. This was defined as the number of patients in each arm experiencing a repeat operation or mastectomy further to initial surgery, within 6 months of randomisation, plus the number of patients who had undergone a pathologically avoidable mastectomy at initial operation in each arm divided by the total number of patients in each arm.

Secondary outcome measures included: factors associated with discrepancy between imaging findings and histopathology; the effectiveness of imaging in terms of agreement with histopathology; change in clinical management following MRI; the rate of chemotherapy, radiotherapy and additional adjuvant therapy interventions; the clinical significance of MR-only-detected lesions; the ipsilateral tumour recurrence rate; patient quality of life (QoL); and cost-effectiveness.

The economic evaluation considered costs from the perspective of the NHS and assessed outcomes in terms of health-related quality of life (HRQoL), based on the EQ-5D, and clinical outcomes. It was planned that if differences in clinical outcome (particularly survival and cancer recurrence) emerged during the trial follow-up period, extrapolation modelling would be undertaken to express these differences in terms of quality-adjusted life-years (QALYs) and costs.

Results

In total, 1623 patients were consented and randomised between December 2001 and January 2007 (816 MRI, 807 no MRI). No differences in the reoperation rate were found between the two groups of patients [MRI patients 18.75%, no-MRI patients 19.33%, difference = 0.58%, 95% confidence interval (CI) –3.24 to 4.40], and the addition of MRI to conventional triple assessment alone was not found to be statistically significantly associated with a reduced reoperation rate (odds ratio = 0.96, 95% CI 0.75 to 1.24, $p = 0.7691$).

Overall, the best agreement between all imaging modalities and histopathology with respect to tumour size and extent of disease was found in patients who were over 50, had ductal tumours NST (no specific type) and who were node negative. Considering the effectiveness of imaging, the sensitivity and positive predictive values of MRI (with regard to determining patient management) were 50.0% (95% CI 42.65 to 57.35) and 61.8% (95% CI 53.87 to 69.74), respectively, and, of the 58 patients undergoing a mastectomy, in the MRI arm 16 (27.6%) were classed as being pathologically avoidable. Weighted kappa statistics ranged from 0.3803 for USS to 0.4767 for MRI when assessing agreement between imaging methods and pathology.

No significant differences were identified in the proportion of patients receiving chemotherapy, radiotherapy or additional adjuvant therapies between the groups ($p = 0.3699$, $p = 0.7439$, $p = 0.5591$). None of the 25 patients with MR-only-detected < 5-mm lesions had a clinically significant lesion evident at their 12-month repeat MR scan. Of the 66 patients with MR-only-detected ≥ 5-mm biopsy-negative lesions, only three had potentially clinically significant lesions at their 12-month repeat MR scan; however, this was based on overall lesion score as these lesions were not biopsied.

Kaplan–Meier estimates of the local recurrence-free interval rate at 1 year were 99.87% (95% CI 99.05 to 99.98) for patients randomised to MRI, compared with 99.73% (95% CI 98.93 to 99.93), for patients randomised to no MRI. No differences in QoL were seen between the two groups of patients [as measured by Functional Assessment of Cancer Therapy-Breast (FACT-B)].

It proved possible to develop a reliable and acceptable NSSI for use in this population of patients. There were high levels of satisfaction and reassurance in patients randomised to receive MRI, despite reported levels of distress secondary to the procedure.

The economic analysis was consistent with the clinical findings that there was no difference in outcomes between the trial arms. Data analysis at 12 months post initial surgery showed no statistically significant difference in HRQoL between the arms, as measured by the EQ-5D. Thus the addition of MRI to the conventional triple assessment is likely to result in extra resource use with few or no benefits in terms of resource saving or HRQoL.

Conclusions

The COMICE study was the first large pragmatic trial evaluating the effectiveness of MRI of small breast lesions, suitable for WLE. The results have shown that although MRI does improve localisation of the tumour, the addition of MRI to triple assessment in women with small breast tumours, does not result in a reduction in reoperation rates.

These results are important from both a health economic aspect, and also from a patient burden aspect. MRI is an expensive procedure. The findings of this trial are of benefit to the NHS and this population of patients by demonstrating that this additional procedure is not necessary, thereby allowing time and resources to be more effectively used elsewhere.

Implications for practice

The addition of MRI to triple assessment in women with small breast tumours, does not result in a reduction in reoperation rates.

Preoperative biopsy of MR-detected lesions only, prior to surgery, is likely to minimise the incidence of inappropriate mastectomy.

Research recommendations

Acceptance of 'close' surgical margins The cosmetic outcome of breast-conserving surgery is often suboptimal, and it is now recognised that more extensive surgery may have little long-term clinical benefit, as residual disease may be adequately treated with standard adjuvant therapy. Future trials need to consider the adequacy of accepting 'close' surgical margins followed by adjuvant therapy on the local recurrence-free interval.

Improved specificity of MRI To improve specificity, consideration needs to be given to: alternative MR sequences, improvement in signal–noise ratio and uniformity of fat suppression. Imaging at 3.0 T may potentially improve specificity, reducing the necessity for biopsy of equivocal lesions and aid the evaluation of ductal carcinoma in situ (DCIS).

Transfer of imaging data Mechanisms for utilisation of two- and three-dimensional MRI data for preoperative tumour mark-up and surgical management need further evaluation.

Alternative treatment options Technological advances have fuelled interest in the use of minimally invasive, image-guided tumour ablation techniques for small tumours, but successful ablation of the entire tumour will require accurate tumour volume delineation.

Trial registration

This trial is registered as ISRCTN57474502.

Chapter 1
Introduction

Overview

This report is divided into seven chapters. The first, the introduction, sets out the complexity of the area and outlines the need for this trial. The second chapter describes the methodology of the main trial and the sub-studies [health economic, quality of life (QoL) and non-schedule standardised interview (NSSI) (well-being)], and the third chapter presents the results of the main trial. The QoL substudy findings and the NSSI study results are presented in the fourth and fifth chapters respectively, and the health-economic analysis results are presented in the sixth chapter. The final chapter provides a discussion of the empirical findings and recommendations for future research.

Triple assessment of the breast

Patients with a screen detected abnormality of the breast, or who present symptomatically, will typically undergo triple assessment. Triple assessment involves clinical examination of the breasts; radiological assessment using X-ray mammography and ultrasound (USS); and pathological assessment either by fine needle aspiration cytology (FNAC) or core biopsy of the suspicious lesion. X-ray mammography relies on the detection of abnormal microcalcifications, focal asymmetric densities and the presence of architectural distortion, created by the variable absorption of X-rays by normal and abnormal tissues. However, it is not diagnostic if the typical characteristics of a malignant process are absent or if the lesion is an encapsulated fat-containing lesion defining a benign process.

Malignant lesions are more difficult to detect in the mammographically dense breast because of technical factors, including reduced image contrast, unsharpness and the similarity in density between cancer and normal fibroglandular elements. This issue may be reduced in the future with the use of full-field digital mammography, which is currently replacing conventional film screen mammography. Large international multicentre studies[1] have demonstrated an equivalent or superior detection rate of breast cancer by digital mammography in comparison with conventional mammography, especially in dense breasts, premenopausal and perimenopausal women, and in women under 50 years of age.

Clinical and surgical management of early breast cancer

It is generally accepted that a patient's best chance of a successful treatment outcome is the accurate identification of the cancer burden present. This means the identification of all tumour foci present and their location and extent. Failure to detect the additional tumour burden provided by multiple small foci may understage the disease present and deny the patient the opportunity of adjuvant therapies if the contribution of the smaller foci is ignored. However, if tumour extent can be delineated accurately, breast conservation, even for those with macroscopically multiple synchronous ipsilateral tumours, is an effective treatment.[2] Local recurrence after conservation surgery usually results from growth of residual cancer adjacent to the excised primary tumour or from multicentric disease.[3–6] Complete local excision, confirmed histologically, is essential to ensure that the risk of local recurrence is minimal. It is now recognised that for patients with multicentric disease detected prior to surgery, breast conservation surgery may still be appropriate if all clinically and radiologically apparent abnormalities are removed, clear margins of resection are achieved, and there is no extensive intraductal component present.

Whilst conventional triple assessment has a high sensitivity for the diagnosis of symptomatic breast cancer, it has limitations in defining the extent of disease present within the breast. For example, Van Goethem *et al.*[7] reported on the results of 67 preoperative breast examinations carried out to predict the extent of cancer in patients with dense breast tissue or to determine whether dense breast parenchyma would lead to false-positive or inconclusive examinations. The sensitivity values

for detection of the index lesion were 83.0% for X-ray mammography (XRM) and 70.8% for USS, with XRM underestimating the extent of cancer present in 37% and USS in 40% of cases. The detection rates for multifocal or multicentric disease (in 20/67 patients) were 35.0% XRM and 30.0% USS, and the false-positive rates were 12.5% and 14.0%, respectively.

The selection of patients for wide local excision (WLE) is dependent on the clinical and imaging findings, namely the site and size of the tumour relative to the breast size. Important excluding factors include: lesions greater than 4 cm in diameter; multifocal or multicentric disease; an extensive in situ component; widespread lymphovascular invasion on biopsy; and centrally placed tumours in small breasts. The Milan II trial,[8] which compared quadrantectomy versus WLE, both followed by radiotherapy, demonstrated that although cosmesis was improved in the WLE group, this was at the expense of a marked increase in loco-regional recurrence (18.6% versus 7.4% 10-year crude cumulative incidence) due to increased incidence of positive excision margins (16% versus 4% in the quadrantectomy group).

The aim of WLE is to remove the palpable lesion with a 1-cm margin of surrounding normal tissue. Using fingers as a guide, the surgeon makes an incision circumferentially, a finger's breadth away from the palpable mass and continues this posteriorly through the breast tissue until the pectoral fascia is reached. If the lesion is not palpable, the mass is located by wire localisation and incision made parallel to the long axis of the wire, and extended to encompass the lesion within a cylinder of tissue. After excision the specimen is marked in three axes and X-rayed to demonstrate the location of the tumour with respect to surrounding excision margins. If the tumour lies at the edge of the specimen and appears incompletely excised, further shavings from the excision cavity are obtained and appropriately marked for pathological verification. It must be noted that at some institutions this is carried out routinely, regardless of whether or not the excision is complete.

The positivity of the margins and the width of the negative margin correlate with the likelihood of residual cancer, whether invasive or in situ, remaining within the breast post WLE. As radiotherapy reduces the ipsilateral breast tumour recurrence rate by a factor of four, resulting in a 75% local control rate, the concept of 'close' margins, with tumour extending to within 1–2 mm of the edge of the specimen, has gained increasing acceptance.[9–12] However, it is likely that the residual tumour burden decreases with increasing margin width, and, as a consequence, the margin width deemed acceptable varies between centres and will drive the need for further local treatments.

Reoperation rates

In 2006–7 some 17% of women in the UK with a screen detected pathologically proven tumour underwent more than one therapeutic operation.[13] This value ranged within the UK from 13% to 21%, but was similar for invasive and non-invasive cancers at 16% and 17%, respectively.

In the UK, 9% (range 6–15%) of patients with invasive cancer with a B5b (invasive malignancy) preoperative diagnosis, who were initially treated with a conservative operation, had a repeat conservative operation to clear positive margins. Patients with invasive cancers with a C5 (malignant) cytology-only preoperative diagnosis who were initially treated with conservative surgery, had a repeat operation rate of 12% (range 8–22%) to clear involved margins, and 16% of patients (range 11–24%) with non-invasive and micro-invasive cancer with a B5a (in situ malignancy) preoperative diagnosis had a repeat operation. Patients with invasive cancers with a B5a preoperative diagnosis, treated initially with conservative surgery, had a repeat operation rate of 31% (range 19–54%). Overall, 12% of all patients with breast cancer, who had a preoperative diagnosis, treated initially by conservative surgery, had repeat conservation surgery for positive margins.

Additionally, in the UK, 6% of patients with invasive cancer with a B5b preoperative diagnosis, 7% of patients with invasive cancers diagnosed by C5 cytology alone, 10% (range 3–15%) of patients with non-invasive cancer with a B5a diagnosis and 20% (range 11–30%) of patients with invasive cancer with a B5a diagnosis underwent mastectomy for positive margins following initial conservative surgery. Overall in the UK, 7% of all patients with a preoperative diagnosis, treated initially by conservation surgery, subsequently underwent mastectomy to achieve tumour clearance.

Thus in 2006/7, 19% of all patients with breast cancer, who had a preoperative diagnosis and who were initially treated by conservative surgery, had

repeat therapeutic procedures (conservative surgery or mastectomy) to achieve clear margins.

The corresponding data from the Association of Breast Surgeons at the British Association for Surgical Oncology (ABS at BASO) for screen detected malignancies for 2001–2 showed that of the 5287 patients with invasive cancer with a preoperative B5b core biopsy, 624 (12%) underwent a repeat therapeutic operation. This varied from 8% to 17%. In the group of patients with invasive cancer diagnosed preoperatively by cytology alone, 15% (range 2–30%) underwent a repeat therapeutic operation. In the group of patients with invasive cancer with a preoperative B5a core biopsy, 41% (range 27–62%) underwent a repeat therapeutic operation.

In the UK as a whole, 14% of patients with invasive cancer and 20% of patients with non-invasive cancer underwent more than one therapeutic operation in 2001–2. For patients with invasive cancers, a repeat therapeutic operation was necessary for 12% of those with a B5b preoperative core biopsy sample, 15% of those with a preoperative diagnosis by fine needle cytology alone, and 41% of those with a B5a preoperative core biopsy.

Thus in 2001–2, at the time of initiation of the COMICE trial, overall a total of 14.2% of women underwent a repeat therapeutic operation for positive margins post WLE.

The figures quoted above relate to patients with a screen detected malignancy. The UK NHS Breast Screening Programme (NHS BSP) invites women between the ages of 50 and 65 years to attend for screening every 3 years, and screening is available for women over 65 years of age if they self-refer. Detection rates are not available for the self-referring population of patients who present with symptoms that are subsequently found to be due to malignancy. Studies suggest that there is a difference in characteristics between screen detected and symptomatic tumours. Screen detected cancers are significantly more frequently grade I, less than 10 mm in diameter and node negative, whereas symptomatic cancers are more frequently grade III, greater than 20 mm in diameter and exhibit lymphovascular invasion. Screen detected cancers favour breast-conserving surgery and are associated with a reduced requirement for adjuvant chemotherapy.[14]

Requirement for the COMICE trial

This trial was developed in response to an open call from the NHS Health Technology Assessment programme for research and development in the area of magnetic resonance imaging (MRI) in patients with newly diagnosed breast cancer. One of the objectives of the NHS BSP is to reduce the reoperation rate for patients with screen detected primary breast cancers to below 10%, whilst achieving a good cosmetic result by minimising the volume of tissue removed. As a consequence of the high reoperation rate, the known problems associated with X-ray mammography and USS, and with reference to the available literature on the results of MR breast imaging, the COMICE trial proposed to determine the comparative effectiveness of the addition of MRI to conventional triple assessment to reduce reoperation rates in women with primary breast cancer treated by WLE. The trial hypothesis was that inclusion of three-dimensional MRI data with conventional triple assessment would aid the localisation of tumour within the breast and enable the surgeon to achieve a higher complete tumour excision rate.

Magnetic resonance imaging: review of literature

Magnetic resonance imaging provides high-resolution soft tissue detail in any plane desired and produces both morphological and functional information. There have now been a number of studies examining the role of MRI of the breast in preoperative and problematic cases, which have shown a good correlation between histological and MR measurement of invasive tumour size ($r = 0.93$) compared with mammographic measurement of tumour size ($r = 0.59$). In 1993, Harms *et al.*[15] used a RODEO (Rotating Delivery of Excitation Off-resonance) technique to demonstrate a good correlation between MRI findings and histopathology of lesion margins in patients who have undergone lumpectomy. This work was confirmed 3 years later by Davies *et al.*[16], who used a three-dimensional fast spoiled gradient echo (FSPGR), contrast-enhanced, fat-suppressed sequence and demonstrated an excellent correlation ($r = 0.98$; standard error = 0.34) between the maximum cancer diameter measured by MR and histopathology. This was particularly evident for the largest cancer diameters. This

compared with poorer correlation coefficients and larger standard errors for mammography and USS at 0.46 and 0.45, and 1.04 and 0.78, respectively. Similar data was presented by Ando and colleagues,[17] who demonstrated a good correlation between direct invasion of mammary tissue, satellite nodule formation and intraductal tumour extension with histopathology. In the study by Van Goethem,[7] mentioned previously, the comparative sensitivity of MRI was 98% and tumour size was only underestimated by 12.5%. The detection rate for multicentric disease was 100%, although the false-positive rate was elevated, with respect to XRM and USS, at 23%. The authors concluded that MRI was more accurate than the other modalities in assessing tumour extent and multifocality in patients with dense breasts, but cautioned that coexisting benign disease could lead to false-positive examinations.

A number of studies have now reported that MRI is more accurate than X-ray mammography in depicting multicentric and multifocal disease, intraductal extension associated with invasive cancer and tumour infiltration of the nipple retro-areolar complex. In a comparative study of mammography, USS and MRI, Boetes *et al.*[18] reported underestimation of tumour size by 14% and 18%, respectively, for mammography and USS, while MRI showed no significant difference in size compared with that found at pathological evaluation. MRI also detected all additional tumour foci found at subsequent histopathology compared with detection rates of 31% and 38% by mammography and USS, respectively. Hata *et al.*[19] also examined the ability of dynamic contrast-enhanced (DCE)-MRI to detect intraductal spread of tumour in comparison with USS and mammography. The sensitivity, specificity and accuracy of detection for intraductal spread by DCE-MRI were 66.7%, 64.2% and 65.6%, respectively. Corresponding results for mammography were 22.2%, 85.7% and 50.0%, and 20.6%, 85.2% and 50.0% for USS, suggesting that DCE-MRI offers a benefit over other imaging modalities for loco-regional staging.

Magnetic resonance imaging: techniques and protocols

Magnetic resonance imaging allows the acquisition of high-resolution anatomical and morphological information, as well as functional information. Functional information can be acquired using DCE-MRI, which refers to the acquisition of data before, during and after intravenous contrast agent administration. As the contrast agent enters the tissue under investigation, the T1 and T2 relaxation times of tissue water decrease over time to an extent mostly determined by the concentration of contrast agent present. This technique is employed to examine neoangiogenically induced vascular changes, which result in the proliferation of abnormally leaky microvessels. DCE-MRI methodology is based on the rapid diffusion of a small molecular weight contrast agent through the fenestration present in these abnormal microvessels. Comparative studies have demonstrated that the signal intensity changes relate to the vascular density within the lesion, and that the rate of enhancement is determined by the vascular fenestrations and functional permeability[20–22] and by the interstitial environment, which influences the diffusibility and temporal retention of the contrast agent. By examining the signal intensity time curves, physiological parameters that relate to tissue perfusion, microvascular vessel wall permeability and the extravascular–extracellular volume fraction can be extracted, which may aid characterisation of the underlying pathology.

The ideal DCE-MRI sequence would encompass the following parameters: excellent temporal resolution (< 30 seconds) to optimally define the signal intensity changes over time (the signal–intensity time curve); a volumetric as opposed to a two-dimensional acquisition, allowing the use of thinner slices with no interslice gap to minimise partial volume averaging and inflow effects; isotropic spatial resolution (< 1 mm in plane); excellent uniform fat/water suppression throughout the volume of interest; high sensitivity to the contrast agent with a good dynamic range; and the capability to image both breasts in their entirety in one pass. Such stringent technical requirements are not currently feasible at 1.5 tesla (T) and, as a consequence, compromises must be made either to the temporal or spatial resolution employed or to extent of the breast coverage obtained.

Currently, two approaches have been used to examine contrast uptake characteristics of breast tissue at 1.5 T. Two-dimensional dynamic imaging allows rapid data acquisition at a limited number of slice locations, and hence good delineation of the signal–intensity time curves, and is suitable for investigation of equivocal lesions on mammography/USS. Alternatively, three-dimensional imaging provides the complete coverage of both breasts required for screening,

but with the penalty of decreased temporal resolution and hence poorer delineation of the signal–intensity time curves. Contrast uptake data must be viewed together with morphological information, which may provide additional insight into the nature of the abnormality. For example, in the presence of rapid contrast uptake the presence of spiculation of a mass and rim enhancement is highly suggestive of malignancy, whereas a lobulated lesion with internal septations is suggestive of a fibroadenoma. The American College of Radiologists Breast Imaging Reporting and Data System (ACR BI-RADS)-MRI Lexicon[23] advocates the use of both lesion architecture and enhancement characteristics, and provides a simple descriptor for reporting of MRI findings.

The trade-off between spatial and temporal resolution in DCE-MRI has been investigated by Kuhl.[24] She examined 30 patients with 54 enhancing lesions (26 malignant, 28 benign) at 1.5 T on two separate occasions. A standard dynamic protocol was employed, using a matrix size of 256×256 and a 69-second acquisition time, followed on a separate day by a modified dynamic protocol using a matrix of 400×512 and 116-second acquisition time. Significant difference between benign and malignant lesions, determined using a generalised linear model, were lost using the modified dynamic protocol, although kinetic information from the signal–intensity time curves was preserved and delineation of lesion margins and internal architecture was superior. Receiver operator characteristic curve analysis demonstrated a significantly larger area under the curve (0.945 versus 0.877, $p < 0.05$) for results obtained using the modified dynamic protocol. They concurred that increased spatial resolution increased diagnostic confidence and accuracy and that because of the overlap in contrast kinetics between benign and malignant lesions, the loss of temporal resolution was of no consequence in characterisation of primary lesions for the individual patient.

The diagnostic performance of dynamic contrast-enhanced parameters and morphological features has been further investigated by Goto *et al.*[25] High temporal resolution dynamic three-dimensional gradient echo (6.8 seconds) and high spatial resolution T1-weighted FSPGR sequences (in-plane resolution of 0.68×0.68×1.0mm) were carried out on 190 patients with a positive diagnosis of malignancy on mammography, USS or both, with a total of 204 lesions (144 malignant) and compared for diagnostic performance. The sensitivity and specificity of the morphological criteria were significantly greater than the enhancement criteria ($p = 0.0012$ and $p = 0.0003$, respectively). Statistically significant differences in morphological criteria were also reported between benign and malignant lesions. They suggested that signal intensity–time curves may not be required to diagnose malignant breast lesions. However, despite excellent temporal resolution, kinetic analysis was only performed subjectively, with signal–intensity peak by the 18th of 28 frames being defined as positive for malignancy and continuous increase in signal intensity through all 28 frames as negative. Additionally, slice thickness for the DCE-MRI examination ranged from 3 to 6 mm, depending on breast size, with a matrix of 196×256 and a field of view of 35 cm, limiting the diagnostic potential of the DCE-MRI examination.

In some reports the combination of functional and morphological data has given added diagnostic value. The importance of morphological information was studied in a report from Gibbs *et al.*,[26] who examined the role of MRI in differentiating less than 1 cm diameter benign from malignant lesions, using a high temporal resolution dynamic two-dimensional FSPGR technique (11 seconds) and high spatial resolution post-contrast T1-weighted imaging. Radiological assessment of the post-contrast data provided a diagnostic accuracy rate of 69%, compared with the exchange rate constant calculated from the DCE-MRI data, which revealed a diagnostic accuracy rate of 74%. However, when the information was combined in a logistic regression model, a diagnostic accuracy of 92% was obtained. This would suggest that the morphological features of small lesions are not adequate in isolation for good diagnostic accuracy.

Ultimately, the characteristics of larger mass lesions compared with small localised abnormalities or areas of diffuse regional enhancement are different and consequently the composition of the patient cohort has a huge impact on the diagnostic accuracy of each study reported. Summarising the available information, the protocols used for loco-regional staging of known or suspected malignancy and those for characterisation of equivocal lesions and screening have different requirements. The latter clinical scenario is potentially diagnostically more challenging, and 'high-quality' functional and morphological information is required to achieve clinically useful accuracy rates.

Role of magnetic resonance imaging for screening

There are now a number of reports advocating the use of MR breast imaging in screening women with *BRCA1*, *BRCA2* or *TP53* gene mutation, or those with a high risk of developing breast cancer from the family history. In general, this patient group is most likely to present with small localised abnormalities or areas of diffuse regional enhancement. The UK multicentre study (MARIBS) of such a patient group, conducted over a 7-year period, utilised a three-dimensional volume acquisition repeated at 90-second intervals to generate functional data and ensure whole breast imaging, followed by a high spatial resolution fat-suppressed sequence for morphology.[27] This protocol resulted in an overall sensitivity and specificity of 77% [confidence interval (CI) 60% to 90%] and 81% (CI 80% to 83%), respectively, for MRI, compared with 40% (CI 24% to 58%) and 93% (CI 92% to95%) for mammography, representing a highly significant improvement in detection by MRI ($p < 0.01$), but significantly poorer specificity ($p < 0.001$). The improved detection rate of MRI compared with mammography was even more apparent for patients with the *BRCA1* mutation or first-degree relatives of patients with *BRCA1* mutation, in whom the sensitivity was 92% (CI 64% to 100%) compared with 23% (CI 5% to 54%), $p < 0.004$, for mammography.

In 2005, Kuhl,[28] using a similar three-dimensional protocol, reported on a surveillance cohort study of 529 asymptomatic *BRCA* patients (proven or suspected from their family history) with a lifetime risk of breast cancer of greater than 20%. In total, 1542 surveillance rounds were performed, with a mean follow-up period of 5.3 years. They detected 43 breast cancers [34 invasive, nine ductal carcinoma in situ (DCIS)], resulting in sensitivity and specificity values of 91% and 97.2%, respectively, for MRI, compared with 33.0% and 96.8% for mammography, and 40.0% and 90.5% for USS. Trecate *et al.*,[29] in a smaller study of 116 patients screened annually using mammography, USS and MRI over a 5-year period, detected 12 cancers of which six were only detected by MRI. In this study there were three false-positive results for MRI but no false-positive results for other techniques.

Role of magnetic resonance imaging for DCIS

Dynamic contrast-enhanced magnetic resonance imaging has also been employed to investigate suspicious microcalcifications on mammography, present either in isolation or associated with a breast mass. In a study of 88 patients, DCE-MRI was used to investigate women recalled following screening mammography for further evaluation of microcalcifications.[30] Dynamic contrast-enhanced imaging data acquired using a high temporal resolution (11 seconds) FSPGR sequence, was analysed using a two-compartment modelling technique, resulting in sensitivity, specificity, positive predictive value, negative predictive value and accuracy values of 80.0%, 82.4%, 57.1%, 93.3% and 81.8%, respectively. These compared with corresponding values of 75.0%, 89.7%, 68.2%, 92.4% and 86.4% if the data were examined by a radiologist using empirical data and lesion morphology together, indicating the benefit of functional information in this patient group.

Bazzocchi *et al.*[31] used a three-dimensional gradient echo dynamic sequence acquired coronally at a temporal resolution of approximately 60 seconds, to investigate 112 patients with mammographically detected microcalcifications with BI-RADS pattern 4 or 5. All subsequently underwent surgical resection and the findings were compared. Analysis of microcalcifications, either alone or in association with a mass, resulted in sensitivity values of 80% and 97%; specificity values of 79% and 33%; positive predictive values of 86% and 82%; negative predictive values of 71% and 75%; and accuracy values of 80% and 82%, respectively. In a small study of only 14 patients with pure DCIS, Mariano *et al.* used an intensity-modulated parametric mapping technique with the data categorised according to morphological and kinetic criteria from the ACR BI-RADS-MRI Lexicon.[23] Using morphological criteria, 71% of cases were correctly classified, with regional enhancement pattern being most prominent, whereas parametric mapping classified 86% of cases, correctly identifying all intermediate and high-grade DCIS cases.

Diagnostic accuracy of magnetic resonance imaging

The studies detailed above have shown a strong correlation between post-contrast, fat-suppressed

images and histopathology in patients with mammographically detected, biopsy-proven malignancy. However, with the detection of increasingly small lesions, the specificity of MRI becomes crucial to patient management. For example, Kramer *et al.*,[32] using a multiple three-dimensional acquisition technique at 90-second intervals, reported a sensitivity of 89% for detection of malignancy, but 17% of women had an incorrect diagnosis of multicentric disease. Similarly, Balen *et al.*[33] commented on inappropriate mastectomy in up to 28% of patients. This study utilised three-dimensional imaging of the breast at between 60- and 80-second intervals following bolus contrast agent injection. Studies such as these rely on detection of contrast uptake by image subtraction and empirical techniques and it is possible that the reduced temporal resolution, and therefore poor delineation of the contrast uptake curve, may have contributed to the false-positive results. This problem is particularly true of screening trials when spatial and temporal resolution is sacrificed for whole breast coverage. Indeed, the screening trials of women with gene mutations, or those with a high risk of developing breast cancer from the family history,[27] have recommended that second-look USS and/or biopsy confirmation of MR findings is obtained before clinical management is changed from WLE to mastectomy.

Role of magnetic resonance imaging in therapeutic management

Dynamic contrast-enhanced MRI, by detecting the neovascularisation induced by malignant lesions, has already been used to determine the therapeutic approach. Tan *et al.*[34] examined 83 patients who were scheduled for breast conservation therapy and found management to be definitively altered in 18%, with 13% of women undergoing additional surgery. Fischer *et al.*[35] investigated 463 women with 548 cancers, and reported a change in management in 14.3% of women, due to detection of more extensive or multicentric disease. Neither study detected factors that were predictive of alteration in outcome from the patient or tumour characteristics, mammographic results or the timing of MRI.

The MRI protocol developed for COMICE is pragmatic and was based on the available technology in the UK in 2001. As a consequence, the majority of examinations were performed at 1.5 T, using a protocol which provides a temporal resolution of 45 seconds and an in-plane spatial resolution of 1.2 mm × 1.1 mm and a through plane resolution of 4mm. The functional data was complimented by a high-resolution post-contrast T1-weighted sequence (0.4 mm × 0.4 mm in plane; 2.5 mm through plane), acquired either with fat-suppression or contrast enhancement later assessed by image subtraction to provide morphological information.

Of particular relevance to this study is the transfer of imaging information, concerning tumour size and location, to the surgeon. It must be remembered that X-ray mammograms are obtained with the patient erect and the breast compressed, USS is performed with the patient supine and the breast variably compressed by the high-frequency probe, whilst for MRI the patient is scanned prone, with the breasts dependent and the arms outstretched beside the head. Surgery is performed with the patient supine and the arm on the affected side abducted to approximately 90 degrees for access. Thus the patient is variably positioned for all imaging techniques and indeed for surgery, and reliance is placed on the surgeon utilising the images obtained to aid excision. Unlike other surgical specialties, stereotactic localisation of the tumour is not carried out.

Influence of magnetic resonance imaging on quality of life

Unfavourable side effects on health-related quality of life (HRQoL) (or health status) may arise from the process of screening itself, such as pain, discomfort and feelings of anxiety and distress. Several studies have shown that recall because of a false-positive mammogram causes adverse emotional, physical and social effects.[36–39] It is already established that breast MRI can cause significant anxiety before, during and for some weeks after the scan. Some studies have shown that the distress caused by MRI is comparable to that caused by elective surgery, and others have found that MRI could not be completed because of anxiety in up to 5% of patients.[40] In a study of 616 women undergoing annual breast MRI because of high genetic risk, MRI-related distress was shown to be greater following breast MRI than X-ray mammography, and persisted in some women for at least 6 weeks after the scan.[41] Anxiety may

be related to multiple factors, including aspects of the procedure (e.g. confinement and noise) as well as context (e.g. fear that cancer may be discovered).[40,42–45]

The COMICE trial sought to elicit if the addition of MRI to triple assessment alone had any impact, negative or positive, on generic HRQoL and distress among women undergoing treatment for breast cancer.

In the main QoL study, two standardised questionnaires, the Hospital Anxiety and Depression Scale (HADS)[46] and the Functional Assessment of Cancer Therapy (breast cancer version) (FACT-B)[47,48] were used to evaluate important generic parameters of HRQoL. The FACT-B questionnaire is a 44-item self-report instrument, designed to measure multidimensional QoL in patients undergoing therapy for breast cancer and has been used extensively in oncology clinical trials, but not specifically in those patients with newly diagnosed breast cancer. Thus to supplement the information obtained from these standardised measures, an NSSI was developed and validated to assess the self-reported psychosocial effects of specific aspects of participation in the COMICE trial, for example reaction to randomisation and the extent to which the various investigations caused distress.

Describing NSSI methodology, Brown and Rutter[49] 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.' The NSSI, therefore, is a flexible quantitative interview method, whereby the interviewer can be flexible about the order and exact wording of questions, as well as in the use supplementary questions for clarification.

Members of the Trial Management Group have previously developed NSSIs for use in two studies. The first evaluated the lifetime care pathways of preschool children with special needs who had been referred to a multidisciplinary assessment centre.[50] 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.[50]

Health economic evaluation

The addition of MRI clearly results in a larger upfront use of health-care resources. However, it is unclear if its addition to conventional triple assessment will result in benefits in terms of better patient outcomes and lower NHS resource use in the future. The key issues with regard to cost-effectiveness from an NHS perspective include: the relative accuracy rates for depicting tumour margins; the uncertainty surrounding the identification of multicentric disease preoperatively; determination of the risk factors for referral for MRI; the impact of MRI on clinical management and patient's QoL; and the medium-term ipsilateral breast tumour recurrence rate.

A review of the literature found no previous cost-effectiveness analyses that have addressed the question of whether the addition of MRI to the routine techniques is worthwhile. The aim of the economic analysis was to compare the costs and consequences (in terms of HRQoL) of the two alternative imaging strategies considered in the COMICE trial. The economic evaluation was conducted from the perspective of the NHS. The costs considered were those relating to NHS and Personal Social Services resource use, while patient outcomes were intended to be measured in HRQoL using the EuroQol 5 Dimensions (EQ-5D) questionnaire, a standardised instrument for measurement of health outcome.

The COMICE randomised controlled trial sought to determine the potential benefits of the addition of MRI to the routine techniques employed for loco-regional staging of primary breast cancer. The cost-effectiveness of MRI in this clinical setting is unknown and the economic analysis of this trial intended to answer whether the addition of MRI is worthwhile from the perspective of the NHS.

Summary

- In 2001–2, at the time of initiation of the COMICE trial, overall a total of 14.2% of women underwent a repeat therapeutic operation for positive margins post WLE. This exceeds the NHS BSP target of 10%.

- Conventional triple assessment has a high sensitivity for the diagnosis of symptomatic breast cancer, but it has limitations in defining the extent of disease present within the breast.
- Magnetic resonance imaging of the breast in preoperative and problematic cases, has shown a good correlation between histological and MR measurement of invasive tumour size.
- The trial hypothesis was that inclusion of three-dimensional MRI data with conventional triple assessment would aid the localisation of tumour within the breast and enable the surgeon to achieve a higher complete tumour excision rate.
- Health economic assessment addressed the question of whether a larger upfront use of health-care resources from the addition of MRI to routine techniques is worthwhile. The trial also sought to elicit the impact on generic HRQoL and the level of distress experienced.

Chapter 2
Methods

Objectives

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

The *primary objective* of the study was to evaluate the role of MRI with respect to the repeat operation (conservative surgery) or mastectomy rates following primary excision between those planned by conventional triple assessment, and those planned by a combination of triple assessment and MRI. This included the rates of pathologically avoidable mastectomy at initial operation. An economic evaluation of the cost-effectiveness from an NHS perspective between the two arms also formed part of the primary objective.

The *secondary objectives* of the study included:

1. An investigation of the factors associated with differences in imaging findings and histopathology, which may influence referral for MRI.
2. Evaluation and comparison of the accuracy of loco-regional staging by X-ray mammography, USS and MRI, with reference to the tumour extent determined by histopathology of the resected specimens.
3. Observation of the percentage of patients in whom a change in clinical management was proposed after MRI.
4. Comparison of subsequent chemotherapy/radiotherapy/additional adjuvant therapy interventions between patients receiving MRI and those receiving no MRI.
5. Follow-up of MRI-only-detected lesions that were < 5 mm in diameter at diagnosis, or ≥ 5 mm in diameter, but which were negative on biopsy.
6. Determination of the ipsilateral breast tumour recurrence rate for both groups.
7. An assessment of QoL and patient satisfaction, with management decisions based on either triple assessment or triple assessment combined with MRI.

Trial design

COMICE was a multicentre, randomised, controlled, open, fixed-sample, parallel group trial with equal randomisation, in women with biopsy-proven primary breast cancer, who were scheduled for WLE following triple assessment [clinical, radiological (X-ray mammography and breast USS) and pathological (FNAC/core biopsy)]. Patients were randomised to receive MRI or no MRI. A pragmatic approach to trial design was chosen so that results could be generalisable in clinical practice and to reduce unnecessary protocol-driven trial costs.

The main trial design was also supplemented with a qualitative study, the Well-Being study, involving a sample of 100 patients, in order to assess patients' subjective and objective experiences of the treatment process and the care pathway. This supplemental study included the development and validation of an NSSI to assess the self-reported psychosocial effects of specific aspects of trial participation. Although the trial was referred to as the Well-Being study at sites, and was introduced to patients as such, from here on in, the report will refer to the Well-Being study as the NSSI study as this better represents the nature of the research.

Eligibility

Inclusion criteria

To be included in the study, patients must have:

- been aged 18 years or over
- undergone X-ray mammography (standard mediolateral oblique, craniocaudal, and, where appropriate, paddle/axillary views carried out within the guidelines of the NHS BSP), and USS scanning (using a 7.5- to 13-MHz linear array transducer) during the current treatment episode
- had pathologically documented primary breast carcinoma, either from FNAC or core biopsy
- been scheduled for WLE on the basis of existing results
- provided written informed consent.

Exclusion criteria

Patients were excluded from this study if they:

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

Note: The ALMANAC trial examined the role of sentinel node biopsy in patients with newly diagnosed primary breast cancer. As participation in both studies was thought to be inappropriate, breast surgeons recruiting into the ALMANAC study were excluded from participation in COMICE.

End points

Primary end points

Reoperation rate

The primary clinical end point of the trial was the rate of repeat operation or mastectomy at further operation, within 6 months of randomisation and following primary excision for breast cancer, or pathologically avoidable mastectomy at initial operation. This end point will be termed the reoperation rate, and was compared between the two trial arms.

Economic evaluation

The economic evaluation of the two principles under investigation uses an NHS cost perspective and quantified HRQoL using the EQ-5D instrument. It includes a within-trial cost-effectiveness relating differential costs to HRQoL up to 12 months following initial surgery. Depending on trial results, it was recognised that there might be a need to undertake an extrapolated cost-effectiveness analysis, where longer-term costs and quality-adjusted survival would be modelled on the basis of any difference in trial estimates of recurrence.

Secondary end points

Factors associated with differences in imaging findings and histopathology that may influence referral for MRI

The factors associated with differences in findings between MRI and histopathology, and between mammography/USS and histopathology were assessed. Factors considered were tumour type and grade, breast density (ACR BI-RADS pattern), history of exogenous hormone consumption, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, menopausal status, nodal status and age.

Effectiveness of imaging

Comparison of the imaging findings and subsequent histopathology of the excised specimens was performed with particular reference to:

- number and location of malignant lesions detected (localised/multifocal/multicentric)
- maximum diameter of all foci of invasive/in situ carcinoma present
- location and extent of additional benign or suspicious lesions (localised/multifocal/multicentric).

Change in clinical management

The proportion of patients in whom a change in clinical management (from WLE) was proposed after MRI was assessed.

Chemotherapy/radiotherapy/additional adjuvant therapy interventions

The subsequent use of chemotherapy/radiotherapy/additional adjuvant therapy interventions was compared between the two arms.

Local recurrence-free interval

Local recurrence-free intervals were calculated for the two trial arms. The terminology 'local recurrence-free interval' has been used here rather than 'local recurrence rate'. This is due to the publication of the recent STEEP guidelines,[51] which aim to standardise definitions of breast

cancer clinical trial end points. The end point of 'local recurrence-free interval' best represents this secondary objective of the COMICE trial.

Quality of life and patient satisfaction

Quality of life was assessed using the FACT-B, and anxiety and depression were assessed using the HADS, at baseline prior to randomisation, 8 weeks post randomisation and at 6 and 12 months post initial surgery.

Clinical significance of < 5-mm MRI-only-detected lesions, and ≥ 5mm biopsy-negative MRI-only-detected lesions

The clinical significance of < 5 mm-diameter MRI-only-detected lesions, and ≥ 5mm biopsy-negative MRI-only-detected lesions, not amenable to further preoperative diagnosis, was ascertained from repeated MRI at 12 months post radiotherapy.

Trial conduct

Trial organisational structure

Overall supervision of the trial was provided by the Trial Steering Committee (TSC) (see Appendix 1). The Committee's remit was 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. The committee reviewed, at regular intervals, relevant information from other sources and recommended appropriate action. The committee ensured that the rights, safety and well-being of the trial participants were the most important considerations and prevailed over the interests of science and society. The full TSC terms of reference can be found in Appendix 2.

The Trial Management Group (TMG), led by Professor Lindsay Turnbull as Chief Investigator (Appendix 3), was responsible for study design, protocol development, ongoing management and monitoring, promotion of the study, interpretation of trial results, and publication of the study. In addition, collaborative partners within the TMG had the following responsibilities:

- The Clinical Trials Research Unit (CTRU), University of Leeds, was responsible for database design, case report form (CRF) design, the provision of the randomisation service, day-to-day project management, data management, data quality/monitoring, statistical analysis and ensuring that trial was conducted within the relevant legal, ethical and good practice frameworks.
- The Project Coordinator, who was based at the Centre for Magnetic Resonance Investigations at Hull Royal Infirmary, along with the Chief Investigator, was responsible for the trial budget, recruiting new centres, maintaining recruitment levels, centre participation, and the quality assurance process.
- The Centre for Health Economics, University of York, was responsible for the cost-effectiveness analysis and the design of the relevant CRFs.

Independent monitoring of the trial was undertaken by the Data Monitoring and Ethics Committee (DMEC) (see Appendix 4). The remit of this Committee was to consider safety issues for the trial and relevant information from other sources. The Committee ensured that ethical considerations were of prime importance and reported to the TSC to recommend on the continuation of the trial. The DMEC also reviewed the imaging findings of patients undergoing a mastectomy at initial operation, in conjunction with their histopathology findings. This was to identify any false-positive findings of the MRI, which had led to patients undergoing a pathologically avoidable mastectomy. The full DMEC terms of reference can be found in Appendix 5.

Trial centres

A total of 107 surgeons from the following 45 centres participated in the trial: Barnet Hospital, Blackpool Victoria Hospital, Bristol Royal Infirmary, Castle Hill Hospital Hull, Conquest Hospital Hastings, Crosshouse Hospital Ayrshire, Darent Valley Hospital Kent, Derriford Hospital Plymouth, Diana Princess of Wales Hospital Grimsby, Frenchay Hospital Bristol, George Eliot Hospital Nuneaton, Grantham and District Hospital, Hairmyres Hospital East Kilbride, Hillingdon Uxbridge, Hinchingbrooke Hospital Huntingdon, Hope Hospital Salford, King's College Hospital London, Leeds General Infirmary, Leighton Hospital Chester, Luton and Dunstable Hospital, Maidstone Hospital, Mid Yorkshire Hospitals NHS Trust (Clayton Hospital, Dewsbury and District Hospital, Pinderfields General Hospital, Pontefract General Infirmary), Northwick Park Hospital, Harrow, Nottingham City Hospital, Prince Philip Hospital Carmarthenshire, Princess of Wales Bridgend, Rotherham General Hospital, Royal Bolton Hospital, Royal Hallamshire

Hospital Sheffield, Royal Lancaster Infirmary, Royal Sussex County Hospital Brighton, Russells Hall Hospital Dudley, Scarborough Hospital, St Bartholomew's Hospital London, St James's University Hospital Leeds, St Mary's Hospital, London, University Hospital of North Durham, University Hospital of North Tees, Victoria Infirmary Glasgow, Walsgrave Hospital Coventry, Western General Hospital Edinburgh, Western Infirmary Glasgow, Whiston Hospital, Prescot, York Hospital, Ysbyty Gwynedd Bangor.

Ethical considerations

The trial was 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 was approved by the North West Multicentre Research Ethics Committee (MREC) and the Local Research Ethics Committee (LREC) for each participating centre prior to entering patients into the study.

Informed consent and randomisation

Invitation to participate in the COMICE trial was made at the time at which treatment options were discussed and agreed with the patient. Whilst at the outpatient clinic, women scheduled for WLE were invited to participate in the study by the consultant breast surgeon or the consultant radiologist, and were subsequently given further information, including the patient information sheet (Appendix 6), by the research nurse. Wherever possible, patients were given at least 24 hours to consider participation in the trial. If the patient wished to participate in the trial, the research nurse arranged an appointment to obtain written consent (see Appendix 7 for a copy of the informed consent form). Once eligibility and written informed consent had been confirmed, the research nurse randomised the patient using the CTRU central automated 24-hour randomisation system, to receive either MRI or no MRI. Authorisation codes provided by the CTRU were required to access the service. Since randomisation was performed via the independent, central CTRU system, allocation concealment was maintained.

Randomisation was performed using minimisation incorporating a random element (dynamic allocation using a pre specified computer generated algorithm incorporating an element of randomness). The integrity of the randomisation system was tested on a regular basis. To ensure balanced treatment groups with respect to prognostic factors, the following minimisation factors were incorporated, as recorded at the time of randomisation:

- consultant breast surgeon
- patient's age (< 50 years versus ≥ 50 years)
- breast density (ACR BI-RADS group 1 (type 1 only) versus ACR BI-RADS group 2 (type 2, 3 or 4).

Homogeneously or heterogeneously structured dense fibroglandular tissue in a large percentage of the entire breast volume is the only mammographic or USS finding to date that has helped define a subgroup of patients with multifocal or multicentric disease detected by MRI alone.[35,52] The definition of breast density according to the mammographic pattern followed the criteria stated in the ACR BI-RADS, as follows: type 1 – almost entirely fatty breast tissue; type 2 – scattered fibroglandular tissue; type 3 – heterogeneously dense breast tissue; and type 4 – extremely dense breast tissue.[23]

Blinding

COMICE was an open trial. Since patients either received MRI or no MRI, the nature of the trial prevented masking the randomised intervention.

Assessments/interventions

For details of the stages in the trial process, see the trial flow diagram in *Figure 1*.

Patients randomised to no MRI

Patients who were randomised into the no-MRI arm went on to receive a WLE as scheduled. Following the WLE, patient management and treatment followed local practice.

Patients randomised to receive MRI

Women randomised to receive MRI were rapidly assessed so that surgery was not delayed. The MR images were evaluated by a consultant radiologist who had prior knowledge of the results of clinical examination, and the results were presented to

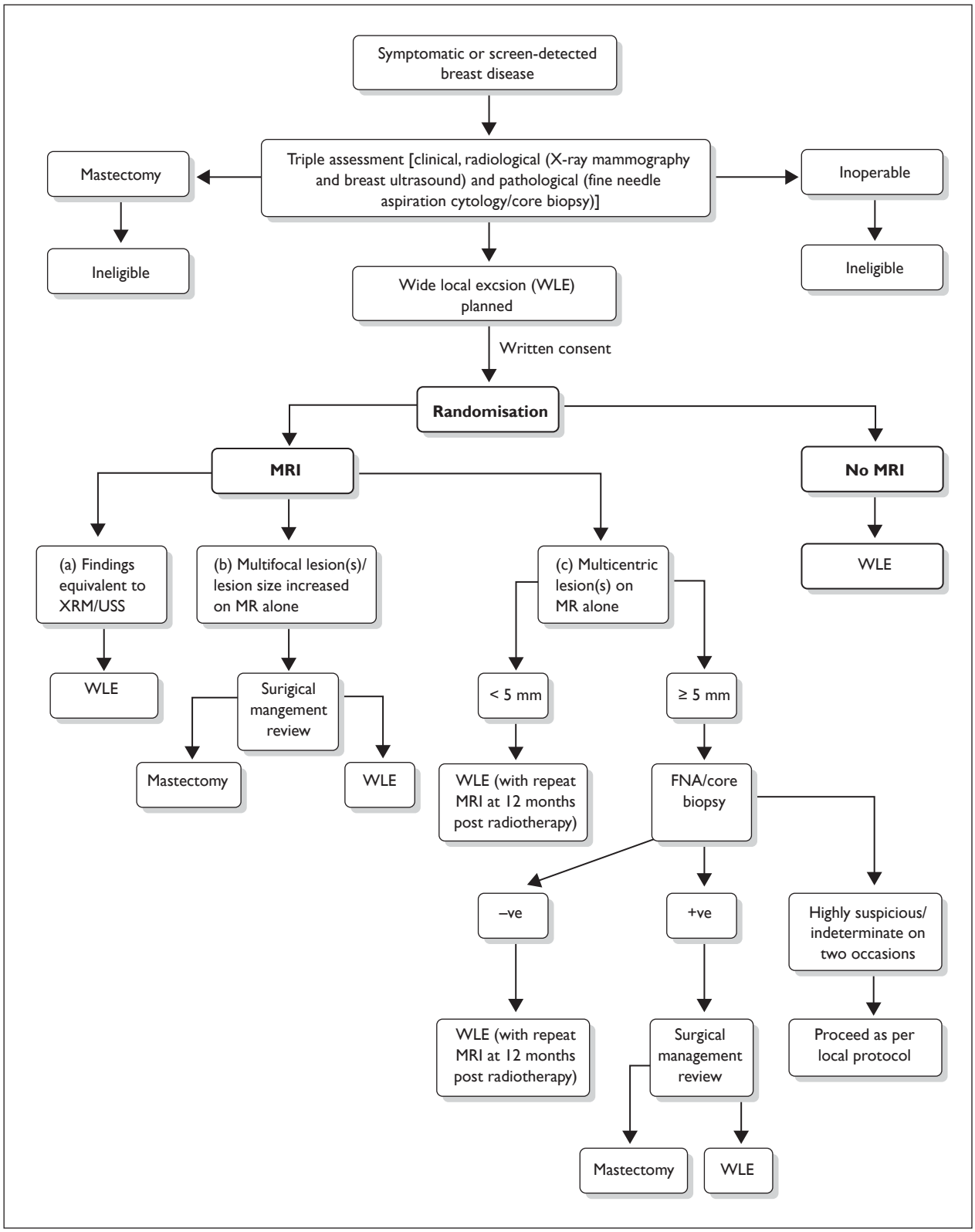

FIGURE 1 *Trial flow diagram.*

the multidisciplinary meeting. The three possible outcomes following review of the mammographic, USS and MRI findings were as follows:

1. Magnetic resonance imaging findings were equivalent to X-ray mammography and USS: patients proceeded, as planned, to WLE.
2. Multifocal lesion(s) were present or the tumour extent was greater than that detected on X-ray mammography and/or USS: surgical management was reviewed at the multidisciplinary meeting and the patient proceeded to WLE, extended WLE or mastectomy as appropriate. In cases of diagnostic difficulty, MR-localised, USS-guided FNAC or core biopsy was recommended for confirmation of findings. (The definition of multifocal lesions was those located within 2 cm of the index tumour.)
3. Multicentric disease was demonstrated by MRI. (Multicentric lesions were defined as those located in a different quadrant of the breast relative to the index tumour.) To obtain whole breast coverage and acquire DCE-MRI data at a temporal resolution of 45 seconds required utilisation of a 4-mm slice thickness. Due to the inevitable partial volume averaging present it was then only possible to analyse lesions that were greater than the MRI slice thickness employed. Morphological information from lesions ≤ 4 mm in diameter is seldom of clinical utility and reported 'miss' rates for cancer for needle-localised breast biopsy range from 0% to 7.9% (mean 2.0%),[53–56] with some evidence of size dependence.[57] As a consequence of the limitations on both the functional and morphological data, a cut-off value for lesion evaluation of 5 mm was employed for management purposes as follows:

   If the multicentric lesion(s) was < 5 mm in diameter. The patient proceeded as planned to WLE.

   If the multicentric lesion(s) was ≥ 5 mm in diameter. The patient underwent MR-localised, USS-guided FNAC/core biopsy or, if available, locally, MR-guided FNAC/core biopsy. If the results were:

   i. *positive for malignancy*, the surgical management was reviewed and the patient proceeded to WLE or mastectomy as appropriate
   ii. *negative for malignancy*, the patient proceeded, as planned, to WLE and was scheduled to receive a repeat MR scan 12 months post radiotherapy
   iii. *indeterminate*, then the patient underwent repeat sampling; patients with indeterminate results on two occasions proceeded according to local protocol, but underwent repeat MRI at 12 months as detailed below
   iv. *suspicious for malignancy* (i.e. C4 or B4) the surgical management was reviewed and the patient treated as per local protocols.

Magnetic resonance imaging at 12 months

Patients with lesions < 5 mm in diameter, or ≥ 5mm in diameter and biopsy negative (or indeterminate), underwent repeat MRI at 12 months post radiotherapy, to assess persistence of change.

Details of magnetic resonance imaging

All imaging was performed on a 1.5-T or 1-T system with a dedicated bilateral breast surface coil for signal reception.

The dynamic contrast-enhanced magnetic resonance imaging method for acquisition of functional information was as follows: multiple thin slice (in plane resolution 1.3 mm × 0.8 mm; slice thickness 4 mm) T1-weighted, three-dimensional FSPGR MR sequences (temporal resolution 45 seconds) were 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 oGd-DTPA/kg body weight).

Morphological information: high-resolution (0.7 mm × 0.4 mm in plane, 2.5-mm slice thickness) precontrast three-dimensional T1-weighted images were obtained coronally to detect areas of post-biopsy haemorrhage and for the purpose of image subtraction if fat suppression techniques were inadequate. High-resolution (0.7 mm × 0.4 mm in plane, 2.5 mm slice thickness) fat-suppressed T1-weighted three-dimensional MR images (allowing maximum intensity projection or multiplanar reformatting) were obtained coronally after contrast administration for morphological information and further sagittal images were acquired if chest wall invasion was suspected. DCE-MRI at 12 months was performed as detailed above. Data analysis included:

1. *Evaluation of the behaviour of the signal intensity–time curve* This was carried out from the most rapid and strongly enhancing region of interest from within any given lesion, taking care to exclude adjacent blood vessels. In centres with workstations these areas were identified semi-automatically by means of parametric images generated by ADVANTAGE WINDOWS or equivalent software packages, which selectively mark and allow pixel-by-pixel interrogation of signal intensity change over time on the anatomical images. Lesions were classified according to morphological appearance and the pattern of the signal intensity–time curve as detailed previously.[58–60] Lesions demonstrating a type I pattern of contrast uptake were considered benign/normal (score 0); type II – indeterminate (score 1); and type 3 – suspicious/malignant (score 2).
2. *Morphological criteria of malignancy* These included ill-defined, irregular or spiculate borders, or peripheral or non-uniform enhancement on high-resolution images. Lesions were classified as 'benign/normal' if none of the above features was present (score 0), 'indeterminate' if all or some of the above features were only partially present or not prominent (score 1) or 'suspicious/malignant' if some or all of the above features were clearly evident (score 2).
3. *Scoring system* A combined score (signal intensity–time curve pattern and morphological information) of two or more was considered suspicious of malignancy, one an equivocal result, and a score of zero equalled a normal/benign result. Each lesion demonstrated was considered independently.

Change in surgical management

Change in surgical management was obtained by comparing the documented treatment option recorded on a study-specific proforma before randomisation with those completed after MRI.

Magnetic resonance imaging data transfer

To facilitate transfer of MRI information, the location and extent of tumour tissue was 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 was marked on hard copy and sent to both breast surgeon and pathologist. A reference copy was retained at the MRI centre.

Data collection

Clinical and resource use data generated by all centres was collected on study CRFs, which were monitored and computerised by the CTRU. Details can be found in Appendix 8.

Using detailed case report forms, information on health-care resource utilisation of the patients in both trial arms were collected at randomisation and during follow-up. These have been supplemented with clinical expert opinion and other additional data where appropriate.

Quality of life

At randomisation, patients were asked if they were willing to take part in the QoL study, in order to evaluate the impact of the investigations and treatment. QoL participation was not compulsory, in order to avoid jeopardising recruitment in to the main MRI study. The FACT-B was used to evaluate the impact on physical, social, emotional and functional well-being, and breast cancer concerns. The FACT-B comprises the FACT-General[48] and 10 specific items related to breast cancer.[47] Anxiety and depression were assessed using the HADS.[46] The EQ-5D was also used to provide a description of patients' HRQoL and HRQoL weights, based on the preferences of a sample of the UK population.[61–63] The EQ-5D is a standardised non-disease-specific instrument that describes and values HRQoL, and provides a single index value for a number of different health states. It is applicable to a wide range of health conditions and treatments, and provides a simple descriptive profile and a single index value for a patient's health status. Its descriptive system consists of five dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression), with each dimension having three different levels (no problem, some problem or extreme problem). All questionnaires were administered together, with the EQ-5D appearing first, the HADS second and the FACT-B third.

Early in the course of the COMICE trial, question GE3 'I am losing hope in the fight against my illness' on the FACT-B was removed from the trial questionnaires, as there was some evidence that it had caused distress to a few patients in the trial

and was not particularly relevant to this recently diagnosed patient population. This does not affect the scalar structure of the questionnaire, and pro-rating was used to compensate for the removal of this item.

Patients were asked to complete QoL questionnaires at the following times: baseline, 8 weeks post randomisation, and at 6 and 12 months post initial surgery. At the start of recruitment in December 2001, and until February 2004, post-randomisation questionnaires were administered at 4 weeks post initial surgery and further questionnaires were administered at 4 weeks post repeat operation (if appropriate). However, it was difficult for the CTRU to obtain initial surgery dates in time to send questionnaires, and some patients underwent repeat operation before their 4 weeks-post-initial-surgery questionnaire was due. As a consequence, the timing of questionnaires was changed, to be administered at 8 weeks post randomisation for all patients thereafter to encapsulate the time period of the initial surgery and any subsequent surgery performed. Post-surgery time points were selected as it was felt necessary to standardise the assessments around the time of surgery, and avoid the possibility of assessments coinciding with actual time of surgery.

Baseline QoL questionnaires were completed by patients in clinic, after written informed consent had been given, and prior to randomisation (or knowledge of randomisation outcome). QoL was then assessed at 8 weeks post randomisation, and at 6 and 12 months post initial surgery by sending questionnaires to the patient's home address (by the CTRU), after the patient's current health status had been checked with the relevant research nurse. Patients who did not respond within 2 weeks of the initial questionnaire being sent were sent a reminder letter; however, if two consecutive sets of questionnaires were not returned, no further questionnaires were sent. A letter of thanks was also sent to patients who returned a set of completed questionnaires.

Data quality and monitoring

Data management and monitoring were conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials[64] and CTRU Standard Operating Procedures. Data management practice included verification, database validation and formal data checking following data entry. All missing and ambiguous data were chased until resolved or confirmed as unavailable.

Statistical methods

Sample size

The sample size calculation was based on the primary end point of repeat operation or mastectomy at further operation, or pathologically avoidable mastectomy at initial operation. At the time the protocol was written, the quality assurance standard for the NHS BSP[65] was less than 10% reoperation rate for incomplete tumour excision, although at the time 14.2% of women aged 50–65 years, with a C5/B5 preoperative diagnosis, underwent more than one operation for primary breast cancer. We therefore assumed that the current reoperation rate for all women with primary breast cancer, who were scheduled for a WLE based on the results of triple assessment alone, was approximately 15%. Assuming that the addition of MRI would reduce this reoperation rate to 10%, a total of 1840 patients were required for this difference to be detected with 90% power, based on a chi-squared test without continuity correction at the 5% two-sided significance level.

No formal interim analyses were planned or conducted during the trial.

Analysis methods

All data analyses were carried out to a prespecified analysis plan. All data analyses of the clinical and QoL end points were performed using SAS version 9.1 (SAS Institute, Carey, NC, USA). All hypothesis testing was performed at the 5% two-sided significance level. Analysis of health economic data was performed using SPSS.

Populations

The intention-to-treat (ITT) population was defined as all patients randomised, regardless of their eligibility, and analyses were conducted according to the treatment that patients were randomised to receive. Only patients who withdrew their consent for the study, or for whom no written informed consent had been obtained, were not included in this population.

The per-protocol population included all eligible randomised patients, according to the treatment they actually received; however, patients defined as major protocol violators were excluded from the per-protocol population. Patients who withdrew their consent for the study, or for whom written informed consent had not been received, were not included in this population.

The QoL population included all randomised patients agreeing to take part in this part of the study, regardless of their eligibility, or who have completed at least one follow-up QoL questionnaire. Patients who withdrew their consent for the study, or for whom written informed consent had not been received, were not included in this population.

During the recruitment period of the trial, an issue arose at one of the centres whereby a higher than average number of patients were not receiving the intervention to which they were randomised, i.e. some patients randomised to receive MRI did not receive an MR scan, and some randomised to 'no MRI' received an MR scan. This issue was brought to the attention of the DMEC and it was decided that the primary end point analysis should be conducted both with and without the data from this centre. Initial analyses were conducted including this centre, and an additional sensitivity analysis was conducted not including the data from this centre.

Primary end point

Reoperation rate

Rate of repeat operation or mastectomy at further operation, or pathologically avoidable mastectomy at initial operation, was the primary clinical end point (termed *reoperation rate*). The rate was defined as the number of patients in each arm experiencing a repeat operation or mastectomy further to initial surgery, within 6 months of randomisation, plus the number of patients who had undergone a pathologically avoidable mastectomy at initial operation in each arm divided by the total number of patients in each arm. A pathologically avoidable mastectomy was defined as either:

- MRI indicated multifocal lesions, resulting in the patient having a mastectomy, but histopathology showed that the extent of the invasive disease was localised, *or*
- MRI indicated an increased size of index lesion, resulting in the patient having a mastectomy, but histopathology showed that either the size of the index lesion or the size of the index and DCIS was 30 mm or smaller.

This definition was specified by an independent DMEC and agreed by the TSC.

Patients with no data regarding the primary end point were those who were either lost to follow-up at the time of the analysis or patients who experienced a mastectomy at initial operation that was either deemed pathologically unavoidable or was carried out due to patient choice alone. Patients who were lost to follow-up or who underwent a pathologically unavoidable mastectomy were classed as not having a primary end point event. Patients for whom the mastectomy at initial operation was carried out due to patient decision alone were classed as having a primary end point event in the main analyses.

The proportion of patients in each arm that had a repeat operation, mastectomy at further operation or pathologically avoidable mastectomy at initial operation, and the difference between the arms, was calculated with corresponding 95% CIs. The chi-squared test, without continuity correction, was used to formally test for a significant difference between the proportions in each trial arm.

Logistic regression was carried out on the primary end point, adjusting for the minimisation factors only. Since there were so many surgeons recruiting to the COMICE Trial (107), many of whom recruited few patients, this variable was recategorised to incorporate surgeons recruiting fewer than 10 patients as one level, and each other surgeon was classed as an individual level. This resulted in surgeon being classed as a categorical variable with 48 levels.

The above analyses were carried out on the ITT and per-protocol populations.

Logistic regression was also carried out including the minimisation factors and other covariates identified as being prognostic of outcome [menopausal status and use of oral contraception or hormone replacement therapy (HRT)].

The proportion of patients in each treatment group that chose to have a mastectomy rather than a WLE, outside the definitions for mastectomy within the trial, was calculated. A sensitivity analysis exploring the impact of these patients on the primary end point was planned, however there were very few patients choosing to have a mastectomy therefore this analysis was not carried out. Sensitivity analyses were also planned to account for patients who were lost to follow-up; however, there were very few patients in this category and so sensitivity analyses were not carried out.

Multilevel modelling was performed adjusting for the minimisation factors age and breast density

and incorporating consultant surgeon as a random effect (random intercept). For this analysis each surgeon represented a different level, therefore surgeon was a 107 level categorical variable. These analyses were carried out on the ITT population only.

Exploratory analyses were also conducted to examine the interactive effect of breast density, menopausal status, tumour grade and tumour type on the effectiveness of MRI compared with no MRI. Tumour type was classed as lobular carcinoma versus all other types, and included patients with invasive carcinoma only, and breast density was categorised as ACR BI-RADS type 1 or 2 versus ACR BI-RADS type 3 or 4. Logistic regression was carried out, including the minimisation factors and the above exploratory factors, and by fitting interaction terms for each of the exploratory factors.

Exploratory analyses were also conducted to identify any interactive effect of lobular carcinoma on the effectiveness of MRI compared with no MRI. A complete case analysis was conducted, therefore patients for whom we could not identify whether or not they had lobular carcinoma were excluded from these analyses. Multivariate analysis was carried out using logistic regression incorporating the minimisation factors, presence of lobular carcinoma, and an interaction term between randomised allocation and whether or not a patient had lobular carcinoma. Patients with lobular carcinoma were then investigated further by considering the correlation between the size of the index lesion via the imaging methods and via histopathology, and by considering the reoperation rates according to treatment arm.

Finally, at the request of the TSC, a further exploratory analysis to examine the interactive effect of age on the effectiveness of MRI compared with no MRI was conducted. Multivariate analysis adjusting for the minimisation factors and incorporating an interaction term between age and MRI was carried out.

Economic evaluation

Economic evaluation of health-care interventions involves combining measures of outcome with resource cost in an attempt to answer whether reallocating resources from one programme to another represents a more efficient allocation of health-care resources. This was evaluated using cost-effectiveness analysis, in which both the costs and consequences of a health-care intervention are compared with those of other relevant comparators.[66] In this study, conventional triple assessment alone was compared with triple assessment combined with MRI.

HRQoL weights of the participants in the COMICE trial were measured using the EQ-5D.

The unit costs considered were those faced by the NHS in terms of health service resource use for 2006–7. The outcomes considered were those experienced by treated patients, which were measured in terms of mortality and HRQoL (based on the EQ-5D questionnaire). Costs and outcomes were measured or extrapolated over the time they could be expected to differ between the two different trial arms.

Unit costs at 2006–7 prices were used to value the resource use measured in the trial where they were available. These were average costs. NHS reference costs have been used for resource use where available, while the *British National Formulary* has been used for the pricing of pharmaceuticals.[67,68] These have been supplemented with data from other sources, most notably the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care.[69] Resource costs were calculated by multiplying resource use by the unit cost.

The EQ-5D consists of five dimensions with three levels each, yielding 243 distinct health states. These health states have been valued on a preference scale, where 0 is equivalent to dead and 1 to full health, using a community sample of people from the UK who valued the health states using the time trade-off technique.[70]

The within-trial analysis involved quantification of the mean resource use and costs during the trial period, as well as estimation of the mean EQ-5D scores at baseline and at different follow-up points. The analysis reported estimates, together with an appropriate measure of sampling uncertainty [e.g. standard deviation (SD)] at different follow-up times in both arms of the trial. There was also a consideration of the characteristics of patients (as defined at the point of randomisation), which explained differences in costs and the EQ-5D; this analysis provided the basis of estimates of the cost-effectiveness of the alternative forms of management in specific subgroups of women.

Depending on the clinical, HRQoL and cost results of the trial, further modelling would be considered

to assess the cost-effectiveness of the alternative forms of management. Specifically, if there were potentially important differences between the trial arms in mortality or the rate of cancer recurrences, modelling of the long-term prognostic implication of this (in terms of women's health and costs) would be undertaken.

Further detail can be found in Appendix 8.

Statistical analysis of health economics data

For each data collection point during the trial, basic descriptive statistics were presented for both resource costs, in total and at disaggregated levels, and EQ-5D scores. These statistics were also calculated for the total resource cost of resources included in the trial analysis during the trial period.

Following the calculation of resource costs and EQ-5D scores for each patient, regression analyses were undertaken. This was conducted with the aim of controlling for other patient-specific covariates that might influence patient costs and/or HRQoL. The aim of this was to help distinguish any treatment arm effects on costs or HRQoL. It also sought to explain variation in patients' costs and HRQoL in terms of the patients' baseline characteristics.

The regression analyses used HRQoL at 12 months post surgery and total costs as the dependent variables. Previous studies have found that costs and HRQoL are both likely to be influenced by the age of the patient, and their body mass index (BMI). HRQoL following treatment has also been found to be highly correlated with the HRQoL score at baseline. Therefore, these variables were included as independent variables in the regression. It was also our a priori belief that a recurrence of cancer would impact significantly on costs and HRQoL and so this was also included as an explanatory variable. Finally, the treatment was also included as an explanatory variable.

The types of data being analysed had specific features. For example, cost data tends to be right skewed, as costs are naturally bounded at zero. To deal with a potentially small proportion of patients with very high costs that might have a larger effect on mean cost than the median, a summary measure of the nature of the distribution (median and lower and upper quartiles) can be employed but may lead to problems with standard regression techniques.[66]

Consequently, as the cost data was unlikely to be normally distributed, estimating the regression using ordinary least squares was thought unlikely to result in best unbiased estimates of the coefficients. Instead, due to cost data being skewed, it was more appropriate to use a general linear model with an identity link and a gamma distribution function. The identity link means that the explanatory variables still act additively on the dependent variable and thus the interpretation of the coefficients is the same as with the ordinary least squares model.[71]

In trials, resource use and EQ-5D data can often be missing for some individuals. If there is a large number of missing observations it may be necessary to impute the data using multiple imputation. This can be achieved using imputation by chained equations (ICE).[72] This involves imputing the values that are missing using the data that are available.

The ICE approach to multiple imputation is based on each conditional density of a variable given all other variables. It does not require the assumption of a multivariate normal distribution, an assumption that would be inappropriate for this trial as the cost data are likely to be positively skewed. When using ICE it is assumed that the data are missing at random or missing completely at random; however, there is clearly the possibility that this might not be the case.

ICE has two major conceptual steps. Firstly, the imputation of a single variable given a set of predictor variables, and, secondly, 'regression switching', which is a scheme for cycling through all of the variables to be imputed. ICE is discussed further in Royston 2004,[72] and was performed using the statistical software STATA following these methods.

Secondary end points

All analyses of secondary end points were conducted on the ITT population (with the exception of the QoL end points, which were conducted on the QoL population only).

Factors associated with differences in imaging findings and histopathology which may influence referral for MRI

The factors associated with differences in findings between MRI and histopathology, and between

mammography/USS and histopathology were assessed. Factors for consideration were tumour type and grade, breast density (ACR BI-RADS), history of exogenous hormone consumption, ER status, PR status, HER2 status, menopausal status, nodal status and age. Patients with missing ER status, PR status, or HER2 status were classed as having 'unknown' status for each corresponding missing variable. Differences in the size of index lesion [histopathology size minus size via method in question (mammography, USS or MRI)] and in extent of disease (i.e. agree/disagree) between the methods were considered. The extent of disease was classed as localised or multifocal/multicentric. Patients with the extent of disease classed as 'not assessable' from histopathology were excluded from the corresponding analyses. Differences between the following imaging methods were considered: MRI and histopathology; mammography and histopathology; USS and histopathology; and mammography *or* USS (whichever method identified the largest tumour diameter) and histopathology.

Selection modelling was used to identify potential factors that might be predictive of differences in findings between the imaging methods and histopathology, which was considered to be the gold standard. Differences between MRI and histopathology could only be considered for those patients who were randomised to receive an MR scan. Forwards stepwise linear regression was used to consider differences in size, and forwards stepwise logistic regression was used to consider differences in extent of disease. The 5% significance level for inclusion into the statistical model was used. Complete case analysis was used for these analyses, i.e. only patients with complete data for each of the potential factors and the end point in question were included. Multilevel modelling was performed on the final statistical models considering MRI compared with histopathology (for size and extent), incorporating radiologist as a random effect variable (random intercept).

Summaries of the imaging method that showed the smallest discrepancy in size compared with histopathology were calculated, where the outcome variable is the method that gave the smallest discrepancy in tumour size compared with histopathology, i.e. mammography, USS or MRI (or combinations of these methods). Discrepancies in size between mammography and USS were summarised descriptively.

Effectiveness of imaging

Agreement of patient management determined separately from the histopathology results and MRI findings was assessed. Patient management was determined with particular reference to: number and type (benign or malignant) of lesions detected; maximum diameter of all foci of invasive or in situ carcinoma or the sum of invasive and in situ carcinoma present; location and extent of additional pathologies (localised/multifocal/multicentric). Determination of patient management was as follows:

WLE occurred when MRI showed:

- localised disease < 30mm *and*
- multifocal or multicentric disease of type unspecified < 5mm *or*
- benign multicentric disease.

Mastectomy occurred when MRI showed:

- multifocal or multicentric malignant disease, *or*
- index lesion ≥ 30 mm.

WLE was classed as being appropriate when histopathology showed:

- localised disease, *and*
- index lesion/invasive lesion plus DCIS < 30 mm.

Mastectomy was classed as being appropriate when histopathology showed:

- multifocal or multicentric malignant disease *or*
- index lesion/invasive lesion plus DCIS ≥ 30 mm.

Agreement of patient management determined by the MRI results and separately from the histopathology results, for patients randomised to receive an MR scan, was assessed according to the above criteria. This determined the numbers of true-positive, true-negative, false-positive and false-negative cases of assessment of lesions by MRI, taking as the gold standard the results of the histopathology, and taking mastectomy to be positive and WLE to be negative. Sensitivity, specificity, positive and negative predictive values were calculated. Patient management determined via MRI and histopathology results was also summarised according to actual patient management. In addition, agreement between MRI and histopathology was summarised by considering identification of additional malignant

lesions, classed as either one or more than one, and compared with the extent of disease as defined by histopathology. One malignant lesion corresponded to localised disease, and more than one malignant lesion corresponded to multifocal or multicentric disease.

Additionally, recurrence data in the histopathology/MRI discrepant groups (patients for whom patient management determined via MRI results was WLE, however management determined via histopathology was mastectomy or vice versa) were examined for indirect evidence of false-negative pathology. For each histopathology/MRI discrepant group the numbers and percentages of patients who had a local recurrence within 1 and 3 years of randomisation were calculated.

Further additional exploratory analyses were conducted to consider the level of agreement in size of tumour between histopathology (the gold standard) and each of the imaging methods, according to tumour stage, and also to consider agreement between the methods to within ± 5mm.

Change in clinical management

Following the MRI, surgical management of the patient was reviewed by the multidisciplinary team. Patients undergoing a quadrantectomy were classed as having a WLE, i.e. no change in patient management. A change to the proposed surgical management was recorded by the named consultant breast surgeon as either conversion to mastectomy or conversion to primary chemotherapy. The percentage of patients in whom a change in clinical management was proposed was calculated as the total number of patients experiencing a change in clinical management divided by the total number of patients in the MRI arm. Patients for whom 'patient decision' was the only reason for mastectomy were classed as having no change in management. Additional findings in the non-randomised breast were also summarised.

Chemotherapy, radiotherapy and additional adjuvant therapy interventions

The proportion of women in the two trial arms who subsequently received chemotherapy, radiotherapy or additional adjuvant therapy (excluding chemotherapy and radiotherapy) interventions was compared using a chi-squared test without continuity correction, for each therapy. Corresponding 95% CIs were calculated for the differences between the arms. Logistic regression was also used to adjust for the minimisation factors, and also to adjust for other covariates that were identified as being prognostic of outcome (menopausal status and use of oral contraception or HRT).

Clinical significance of MRI-only-detected lesions

Patients with lesions that were detected by MRI only, which either measured less than 5mm, or were biopsy negative and measured at least 5 mm in diameter, were subject to a repeat MR scan at 12 months post radiotherapy. The proportion of patients in each of these categories whose lesion was still evident at the repeat 12-month MR scan and was found to be biopsy positive was summarised (defined as the proportion of patients with a clinically significant lesion at 12 months). This was calculated as the number of patients with a clinically significant < 5mm lesion (≥ 5-mm biopsy-negative detected lesion) still evident at 12 months divided by the total number of patients with a clinically significant < 5-mm lesion (≥ 5-mm biopsy-negative detected lesion) identified at baseline.

Local recurrence-free interval

Local recurrence-free intervals at 1-year post randomisation and corresponding 95% CIs were calculated for each of the trial arms. Local recurrence-free interval was defined as the time from randomisation to the date of local recurrence, or time from randomisation to the date of death due to breast cancer. Patients with missing follow-up data, or who were alive and local recurrence-free at the time of analysis, were censored at the last date they were known to be alive and local recurrence free (date of last disease assessment). Kaplan–Meier curves were plotted to obtain point estimates, and Cox's proportional hazards model was fitted to adjust for the minimisation factors, and also for other covariates identified as being prognostic of outcome (menopausal status and use of oral contraception or HRT). No formal hypothesis testing was carried out on this end point, as the trial does not have sufficient power to detect differences in local recurrence-free intervals between the trial arms.

Quality of life

The measurements of QoL being used in this study are the five subscales of the FACT-B (physical, social, emotional and functional well-being, breast cancer concerns), the Total FACT-B score, the Trial Outcome Index (TOI) FACT-B score, and two subscale scores for the HADS (anxiety, depression).

The baseline characteristics of patients taking part in the QoL study were tabulated and informally compared with the baseline characteristics of the ITT population, to ensure that the sample of patients taking part in the QoL study was similar to that for which clinical inferences were being made.

Data were analysed using a time frame of ± 14 days around the expected date of completion of the questionnaire at 8 weeks post randomisation, a time frame of ± 28 days around the expected date of completion of the questionnaires at the 6-months-post-initial-surgery questionnaire and ± 56 days around the expected date of the 1-year-post-initial-surgery questionnaire. Only pre-randomisation assessments (or post-randomisation assessments carried out before the patient was informed of their randomisation result) were included as baseline measurements. Questionnaires were scored according to the criteria set out in the respective manuals. Estimates were calculated for the medians, means and corresponding 95% CIs for the means for each of the summary scale and total scores at baseline, 8 weeks' and 6 and 12 months' follow-up. Line graphs of median data for each treatment group over time were also produced. The HADS questionnaire was also summarised categorically, with anxiety or depression scores of 0–7 indicating that a patient is 'normal' with respect to anxiety or depression, a score of 8–10 indicating that the patient shows 'borderline' signs of anxiety or depression, and a score of greater than 10 indicating that the patient is likely to have 'clinically significant' anxiety or depression.[46]

Quality of life was compared for each treatment arm using adjusted for baseline mean scores and 95% CIs. Multilevel repeated measures modelling was used to account for data at all post-baseline time points, regardless of time window for the time point not of interest. Data was assumed missing at random and the model incorporated fixed effects (time, treatment, treatment–time interaction, baseline QoL) and random effects (patient and patient–time interaction).

Non-schedule standardised interview substudy

Recruitment

At the time of recruitment into the main study, women were given an additional information sheet (Appendix 9) about the NSSI study and were asked by the research nurse if they would be willing to take part. If they agreed, they then gave written consent (Appendix 10). Between 12 and 18 months postoperatively, women who had consented were contacted by the CTRU in Leeds to ascertain if they were still willing to participate. If this was the case, they were asked to indicate a time convenient to them when they would be willing to be interviewed by telephone. The first four women were used to pilot the NSSI. Thereafter, a consecutive series of 100 women (in terms of recruitment date) were then interviewed to achieve as representative a sample as possible.

Development of the NSSI

Topics were identified a priori for inclusion in the NSSI and included various clinical and sociodemographic characteristics, response to randomisation, investigative procedural distress and perceived choice of surgical procedure.

Two consultant clinical psychologists and the research assistant developed a proforma detailing the questions to be asked, and the response categories to be used. Copies of the schedule and response sheet can be found in Appendix 11. Reliability was evaluated in a pilot study in which four women, who were ineligible for inclusion in the main NSSI study because of the date of randomisation, participated. The researcher telephoned them and explained the purpose of the interview. He explained that two clinical psychologists were present and would be listening to the interview. At the end, it was likely that they would ask some questions for clarification. These women were also asked to provide feedback on the interview process. The interviewer and the clinical psychologists independently rated responses to assess inter-rater reliability. Any disagreements were discussed and the proforma altered accordingly. By the fourth interview, the three raters obtained perfect agreement.

The NSSI

Women were telephoned at a time they had indicated would be convenient for them. The researcher explained the purpose of the interview and indicated that it would last approximately 20 minutes. Responses were coded as indicated above and analysed using SPSS version 13 and GRAPHPAD 3.06.

Quality assurance

A total of 45 centres participated in the trial, using 41 MR scanners. This large network of centres was necessary to achieve trial completion in a timely manner. All centres were NHS hospitals with functioning breast cancer multidisciplinary teams. Participating radiologists were members of those teams and routinely used imaging for breast care. A separate quality assurance process was undertaken to ensure that MR scans were being completed in accordance with the technical requirements of the trial protocol, and that scan interpretation was reasonable and consistent across the network.

The re-reading process was undertaken by an experienced breast radiologist, external to the trial, who was vetted and approved by the DMEC. This radiologist, blinded to original findings, advised on the compliance of the scans to the technical protocol, and then re-reported them using the trial forms. Trial staff compared these re-reports to the original radiologist's reports.

Where variations, such as technical failure, non-identification of lesions or identification of additional lesions were detected, these were referred to the chief investigator for a third reading of the scan. In cases where the re-reported scan and the report from the chief investigator concurred, and were at variance to the original radiologist report, then that scan was considered to have been misreported. If technical failures were confirmed, or scans were considered to have been misreported, then up to five additional scans, if available, were re-read.

The process of scan selection for the quality assurance process was divided into two components. These were:

- *Initial assessment* The quality assurance process involved using a questionnaire to assess radiologist experience. 'Less experienced' radiologists were defined as those who had read fewer than 50 MR scans, or had been reading breast MR scans for less than 2 years. The initial two MR scans from 'experienced' radiologists, and the initial four, from those classified as 'less experienced', were re-read for quality assurance.
- *Ongoing assessment* After this initial assessment, a random sample of scans from each centre was re-read to ensure ongoing consistency. Participating centres were defined as either 'large', recruiting at least 12 patients per year, requiring one in every 10 scans to be re-reported, or 'small', recruiting fewer than 12 patients per year, and requiring one in every five scans to be re-reported.

Summary of changes to the protocol

The following protocol amendments were submitted and approved by the HTA: clarification of the definition of multifocal/multicentric lesions; updated information to detail that indeterminate tumours and highly suspicious lesions should be treated as per local protocol; modification of the patient information sheet; removal of question GE3 'I am losing hope in the fight against my illness' from the FACT-B questionnaire; reduction of the quantity of health economic information recorded on the initial surgery CRF; and amendment to the QoL questionnaire schedule.

The following amendments to end point definitions and to the follow-up schedule were also agreed by the TSC and incorporated in the statistical analysis plan, prior to any analysis being performed: the definition of the primary end point has been updated to incorporate pathologically avoidable mastectomies at initial surgery; the secondary end point 'risk factors for referral for MRI' has been clarified to be 'factors associated with differences in imaging findings'; the follow-up schedule has been amended due to the extension to recruitment, to follow up all patients for at least 1 year post randomisation, and, consequently, ipsilateral breast tumour recurrence has been summarised at 1 and 3 years post randomisation. The exclusion criteria were also amended to exclude patients scheduled to receive chemotherapy to any site prior to their breast surgery, and the timing of repeat MR scans was updated to coincide with 12 months post radiotherapy.

Chapter 3
Clinical results

Participant flow

Sample size

In total, 1625 patients were randomised between December 2001 and January 2007, by 107 surgeons across 45 centres. The number of patients recruited per centre ranged from 1 to 213.

In total, 817 patients were randomised to receive DCE-MRI, and 808 patients were randomised to receive no MRI. Please see Appendix 12 for a brief summary of patient recruitment throughout the trial. Although this is below the target sample size of 1840 patients, this still provides us with over 80% power to detect a reduction in reoperation rates of 5%.

Analysis populations

Confirmation of written informed consent could not be obtained centrally for two patients (MRI = 1, no MRI = 1), therefore these patients were not included in the ITT or per-protocol populations.

Intention-to-treat population

No patients withdrew their consent for the study, therefore the ITT population contains a total of 1623 patients (MRI = 816, no MRI = 807). All analyses and summaries for the ITT population are by randomised intervention.

Per-protocol population

Table 1 displays a breakdown of the major protocol violators according to the randomised allocation (these are not mutually exclusive). Major protocol violations were defined by the Chief Investigator prior to analysis, and patients defined as major protocol violators were excluded from the per-protocol population. Patients for whom a bilateral WLE should have been scheduled were identified as those patients who underwent a bilateral WLE and for whom malignant lesions were identified in both breasts via mammography and/or USS. Patients identified as not being scheduled for WLE are patients for whom more than one malignant lesion was identified in the randomised breast via mammography and/or USS, and who underwent a mastectomy at initial operation. There were 45 (2.8%) major protocol violators in total (MRI = 23, no MRI = 22), therefore the per-protocol population consists of 1578 patients. All analyses and summaries of the per-protocol population are by intervention actually received.

Trial conduct

A CONSORT (Consolidated Standards of Reporting Trials)[73] flow diagram of trial progress is presented in *Figure 2*.

No patients withdrew their consent to use data already collected during the trial; however, one patient in the MRI group withdrew from trial follow-up before undergoing their surgery therefore this patient was classed as being lost to follow-up. In total there were 10 patients who were lost to follow-up at the time of analysis (four patients in the MRI group, six patients in the no-MRI group). In the MRI arm, one patient withdrew from follow-up as detailed above, and three patients had missing data at the time of analysis. In the no-MRI arm, two patients moved away and could not be followed up, and four patients had missing data at the time of analysis. Analysis of the primary end point and shorter-term end points was conducted once all patients had been followed up for at least 6 months. Analysis of longer-term end points and health economic analysis was conducted once all patients had been followed up for at least 12 months.

Baseline data

Baseline characteristics, including minimisation details, patient characteristics and clinical details of the ITT population are displayed in *Tables 2–5*. Corresponding details for the per-protocol population are displayed in Appendix 14. The two groups were well balanced with respect to baseline characteristics, and were very similar between the ITT and per-protocol populations.

The minimisation factors consultant surgeon, age and breast density were well balanced across the two arms for the ITT populations, with the

TABLE 1 *Major protocol violations (not mutually exclusive)*

	MR scan, *n* (%)	No MR scan, *n* (%)	Total, *n* (%)
Protocol violations – not mutually exclusive			
Bilateral WLE scheduled	0 (0.0)	3 (0.4)	3 (0.2)
Could not identify actual procedure	2 (0.2)	0 (0.0)	2 (0.1)
MRI before randomisation	1 (0.1)	0 (0.0)	1 (0.1)
No mammography and no USS	14 (1.7)	16 (2.0)	30 (1.8)
No path-confirmed primary breast cancer	0 (0.0)	1 (0.1)	1 (0.1)
Previous chemotherapy/hormonal therapy	1 (0.1)	1 (0.1)	2 (0.1)
Previous surgery to ipsilateral breast	3 (0.4)	0 (0.0)	3 (0.2)
Should not have been scheduled for WLE	4 (0.5)	2 (0.2)	6 (0.4)
Total (*n*)	23	22	45

majority of patients aged 50 or over (77.0%), and with breast density 2, 3 or 4 (87.2%). Patients were recruited to the COMICE trial by 107 consultant surgeons, with 60 (56.1%) recruiting fewer than 10 patients, and 47 (43.9%) recruiting 10 or more patients. The number of patients randomised to each of the interventions was well-balanced according to the number of patients each consultant surgeon had recruited.

The majority of patients in the ITT population were randomised between 2004 and 2006. The median age of patients at randomisation was 57 (range 27–86). At the time of randomisation, 31.9% of patients were employed full time, 23.1% were employed part time, and 32.6% were retired. All other patients were either unable to work due to illness/disability, were unemployed, or were students. Employment status was missing for 12 patients (0.7%). At the time of randomisation, 1139 patients (70.2%) were post-menopausal, with 60.8% of patients currently or previously taking the contraceptive pill/slow release injection. Of those patients taking the contraceptive pill/slow release injection at the time of randomisation, the median time patients had been taking it was 14 years (range 1–32) (MRI: 13 years, range 1–30; no MRI: 15 years, range 1–32). For those patients previously taking the contraceptive pill/slow release injection, the median time that patients had been taking it was 6 years (range < 1–35) (MRI: 6 years, range 1–30; no MRI: 5 years, range < 1–35). Five hundred and seventy-two patients (35.2%) were either currently using HRT (6.7%) or had previously used HRT (28.5%) at the time of randomisation. Of those patients using HRT at the time of randomisation, the median time that patients had been using it was 8 years (range < 1–32) (MRI: 8 years, range < 1–23; no MRI: 7 years, range 1–32). For those patients previously using HRT the median time that patients had been taking it was 6 years, range < 1–30 (MRI: 7 years, range < 1–27; no MRI: 6 years, range 1–30).

Cancer was identified through screening for 847 patients (52.2%) in the ITT population, and the method of confirming primary breast cancer was fine needle aspiration for 146 patients (9.0%), core biopsy for 1260 patients (77.6%) and fine needle aspiration and core biopsy for 204 patients (12.6%). One patient had a confirmatory histological sample taken after randomisation. Only 17 patients (1%) received preoperative neoadjuvant therapy, and, of these, 10 (58.8%) received tamoxifen, three (17.6%) were presribed anastrozole, and four (23.5%) other therapy, namely letrozole (three patients) and FEC (one patient, who received a combination of docetaxol, epirubicin and cyclophosphamide). An additional patient underwent eight cycles of chemotherapy prior to her surgery, but this was not documented at the time of initial assessment prior to randomisation.

Details of the mammography and USS findings for the ITT population are given in Appendix 13, as well as the MRI findings for the ITT population. The corresponding summaries of baseline data and MRI findings for the per-protocol population can be found in Appendix 14. Mammography and USS findings were similar between the two arms.

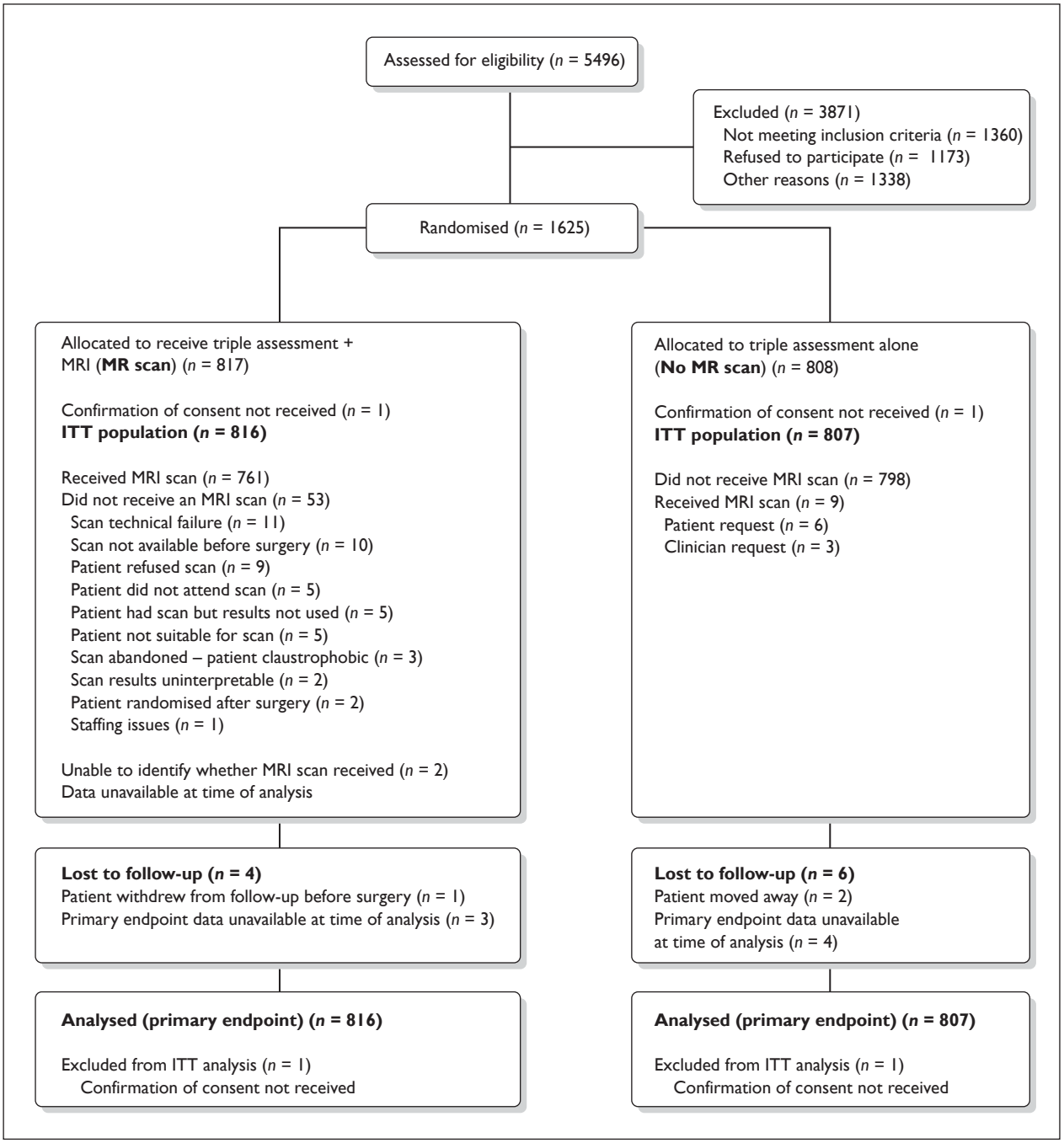

FIGURE 2 *CONSORT diagram. Please note that data regarding numbers of patients assessed for eligibility were not complete for all centres.*

Detailed surgery characteristics are displayed in Appendix 13. The randomising consultant surgeon was present at initial surgery for 1077 patients (66.4%). In total, 1537 patients (94.7%) underwent a WLE at initial surgery, 68 (4.2%) underwent a mastectomy, one (0.1%) underwent a quadrantectomy and mini flap, and two patients underwent other surgery (reduction mammoplasty and segmentectomy). Median time from randomisation to surgery was 13 days (range 1 to 243), and was similar between the two arms. Two patients underwent surgery before randomisation and one patient had eight cycles of neoadjuvant chemotherapy prior to surgery. Axillary surgery was performed on 92.5% of patients and a clear margin was obtained for 94.5% of patients. Twelve patients (0.7%) in total underwent a WLE of the contralateral breast and one patient underwent a

TABLE 2 *Minimisation factors (ITT population)*

	MR scan, *n* (%)	No MR scan, *n* (%)	Total, *n* (%)
Total	816 (100.0)	807 (100.0)	1623 (100.0)
Minimisation factors			
Number of patients recruited by randomised surgeon			
< 10	115 (14.1)	115 (14.3)	230 (14.2)
≥ 10	701 (85.9)	692 (85.7)	1393 (85.8)
Age (as randomised)			
< 50 years	187 (22.9)	187 (23.2)	374 (23.0)
≥ 50 years	629 (77.1)	620 (76.8)	1249 (77.0)
Breast density			
BI-RADS group 1	102 (12.5)	106 (13.1)	208 (12.8)
BI-RADS group 2	714 (87.5)	701 (86.9)	1415 (87.2)

TABLE 3 *Initial clinical details (ITT population)*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
Initial clinical details			
Age at randomisation			
Mean (SD)	56.38 (9.67)	56.59 (10.09)	56.48 (9.88)
Median (range)	57 (27 to 86)	57 (28 to 85)	57 (27 to 86)
n	816	807	1623
Employment (n, %)			
Working full-time	257 (31.5)	260 (32.2)	517 (31.9)
Working part-time	196 (24.0)	179 (22.2)	375 (23.1)
Unable to work due to illness/disability	24 (2.9)	16 (2.0)	40 (2.5)
Retired	260 (31.9)	269 (33.3)	529 (32.6)
At home, not looking for work	57 (7.0)	65 (8.1)	122 (7.5)
Unemployed, looking for work	11 (1.3)	7 (0.9)	18 (1.1)
Student	6 (0.7)	4 (0.5)	10 (0.6)
Missing	5 (0.6)	7 (0.9)	12 (0.7)
Hospital (number of patients recruited) (n, %)			
< 10	54 (6.6)	59 (7.3)	113 (7.0)
10–20	95 (11.6)	85 (10.5)	180 (11.1)
≥ 20	667 (81.7)	663 (82.2)	1330 (81.9)

TABLE 4 *Hormonal characteristics (ITT population)*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
Menopausal status			
Premenopausal	232 (28.4)	234 (29.0)	466 (28.7)
Post-menopausal	574 (70.3)	565 (70.0)	1139 (70.2)
Missing	10 (1.2)	8 (1.0)	18 (1.1)
Contraceptive pill/slow release injection use (n, %)			
Currently	23 (2.8)	28 (3.5)	51 (3.1)
Previously	458 (56.1)	478 (59.2)	936 (57.7)
Never	327 (40.1)	294 (36.4)	621 (38.3)
Missing	8 (1.0)	7 (0.9)	15 (0.9)
How long taken for (years) – currently taking pill (n, %)			
Mean (SD)	12.74 (8.56)	14.78 (8.71)	13.84 (8.61)
Median (range)	13.0 (1.0 to 30.0)	15.0 (1.0 to 32.0)	14.0 (1.0 to 32.0)
Missing	0	1	1
n	23	27	50
How long taken for (years) – previously taken pill (n, %)			
Mean (SD)	8.00 (6.16)	7.47 (6.22)	7.73 (6.19)
Median (range)	6.0 (1.0 to 30.0)	5.0 (0.0 to 35.0)	6.0 (0.0 to 35.0)
Missing	20	21	41
n	438	457	895
HRT use (n, %)			
Currently	63 (7.7)	46 (5.7)	109 (6.7)
Previously	232 (28.4)	231 (28.6)	463 (28.5)
Never	514 (63.0)	528 (65.4)	1042 (64.2)
Missing	7 (0.9)	2 (0.2)	9 (0.6)
How long taken for (years) – currently taking HRT (n, %)			
Mean (SD)	9.82 (5.92)	8.98 (6.86)	9.48 (6.30)
Median (range)	8.0 (0.0 to 23.0)	7.0 (1.0 to 32.0)	8.0 (0.0 to 32.0)
Missing	2	4	6
n	61	42	103
How long taken for (years) – previously taken HRT (n, %)			
Mean (SD)	7.92 (5.70)	7.35 (5.28)	7.64 (5.50)
Median (range)	7.0 (0.0 to 27.0)	6.0 (1.0 to 30.0)	6.0 (0.0 to 30.0)
Missing	6	11	17
n	226	220	446

TABLE 5 *Identification and preoperative therapy (ITT population)*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
Identification and preoperative therapy			
***Cancer identified through screening* (n, %)**			
Yes	415 (50.9)	432 (53.5)	847 (52.2)
No	397 (48.7)	372 (46.1)	769 (47.4)
Missing data	4 (0.5)	3 (0.4)	7 (0.4)
Method of confirming primary breast cancer (n, %)			
FNA	67 (8.2)	79 (9.8)	146 (9.0)
Core biopsy	632 (77.5)	628 (77.8)	1260 (77.6)
Both	112 (13.7)	92 (11.4)	204 (12.6)
Missing	5 (0.6)	8 (1.0)	13 (0.8)
Time from confirmatory histological sample to randomisation (days)			
Mean (SD)	14.08 (7.83)	14.15 (8.79)	14.11 (8.32)
Median (range)	13.0 (0.0 to 49.0)	14.0 (–24 to 94.0)	13.0 (–24 to 94.0)
Missing	8	10	18
n	808	797	1605
Preoperative neoadjuvant therapy (n, %)			
Yes	6 (0.7)	11 (1.4)	17 (1.0)
No	808 (99.0)	792 (98.1)	1600 (98.6)
Missing data	2 (0.2)	4 (0.5)	6 (0.4)
Type of therapy (n, %)			
Tamoxifen	4 (66.7)	6 (54.5)	10 (58.8)
Anastrozole	2 (33.3)	1 (9.1)	3 (17.6)
Other	0 (0.0)	4 (36.4)	4 (23.5)

mastectomy of the contralateral breast (in the MRI arm).

Pathological findings are displayed in *Tables 6–8*, and it can be seen that the findings are very similar between the two arms. Additional findings (Appendix 13, *Table 43*, Pathology: predictive markers) are given in Appendix 13. The median weight for WLE specimens was 52.8 g (range 5.0–770.0) and for mastectomies was 842 g (range 217–2415). In total, 1154 patients (71.1%) had carcinoma in situ (CIS), 1466 patients (90.3%) had invasive carcinoma and 91 patients (5.6%) had DCIS alone. An additional patient had lobular carcinoma in situ (LCIS) alone. Of the 1466 patients with invasive carcinoma, 1114 patients (76.0%) had ductal NST, and 133 (9.1%) had lobular carcinoma. 1244 patients (84.9%) had localised disease and 179 patients (12.3%) had multifocal or multicentric disease. Extent of disease was not assessable for 16 patients (1.1%). Nodes were examined for 1470 patients (90.6%). Details of predictive markers are given in Appendix 13. Overall, 1242 patients were ER positive (76.5%) and 225 (13.9%) were ER negative; 823 patients (50.7%) were PR positive and 331 (20.4%) were PR negative; while the HER2 status was known in 665 (41%) patients, of whom 444 (66.8%) had a score of 0.

Primary end point

The primary end point of the trial was the rate of repeat operation or mastectomy at further operation, within 6 months of randomisation, or pathologically avoidable mastectomy at initial operation (termed *reoperation rate* from now).

TABLE 6 *Pathology: specimen demographics and sampling*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
Specimen demographics and sampling			
Weight of specimen (g)			
Mean (SD)	114.6 (225.7)	66.76 (74.36)	90.73 (169.8)
Median (range)	56.0 (5.9 to 2415.0)	52.0 (5.0 to 1337.0)	54.0 (5.0 to 2415.0)
Missing	81	75	156
n	735	732	1467
Weight of specimen (g) – WLE			
Mean (SD)	70.55 (54.63)	63.69 (52.11)	67.05 (53.45)
Median (range)	54.0 (5.9 to 395.0)	51.0 (5.0 to 770.0)	52.8 (5.0 to 770.0)
Missing	55	62	117
n	695	725	1420
Weight of specimen (g) – mastectomy			
Mean (SD)	931.0 (504.3)	807.3 (458.9)	921.7 (496.6)
Median (range)	850.0 (217.0 to 2415.0)	557.0 (528.0 to 1337.0)	842.0 (217.0 to 2415.0)
Missing	21	7	28
n	37	3	40
Number of blocks taken			
Mean (SD)	14.87 (8.42)	14.21 (8.71)	14.54 (8.57)
Median (range)	13 (1 to 60)	12 (0 to 78)	13 (0 to 78)
Missing	160	143	303
n	656	664	1320
Number of blocks through tumour			
Mean (SD)	5.11 (3.72)	4.78 (2.90)	4.95 (3.34)
Median (range)	4 (0 to 51)	4 (0 to 21)	4 (0 to 51)
Missing	234	227	461
n	582	580	1162
Number of nodes examined			
Mean (SD)	8.98 (6.22)	8.71 (6.79)	8.85 (6.51)
Median (range)	7 (1 to 42)	6 (0 to 59)	7 (0 to 59)
Missing	0	2	2
n	744	724	1468
Number of nodes involved			
Mean (SD)	0.69 (2.09)	0.98 (3.39)	0.84 (2.81)
Median (range)	0 (0 to 28)	0 (0 to 51)	0 (0 to 51)
Missing	0	1	1
n	744	725	1469

TABLE 7 *Pathology: in situ disease*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
In situ disease			
***CIS present* (n, %)**			
Yes	586 (71.8)	568 (70.4)	1154 (71.1)
No	191 (23.4)	193 (23.9)	384 (23.7)
Missing	39 (4.8)	46 (5.7)	85 (5.2)
***CIS pathology* (n, %)**			
DCIS: high grade	249 (42.5)	246 (43.3)	495 (42.9)
DCIS: other	282 (48.1)	276 (48.6)	558 (48.4)
LCIS	47 (8.0)	38 (6.7)	85 (7.4)
Missing	8 (1.4)	8 (1.4)	16 (1.4)
Size of CIS (mm)			
Mean (SD)	16.14 (18.47)	14.84 (13.92)	15.49 (16.35)
Median (range)	10.0 (0.0 to 130.0)	11.0 (0.2 to 79.0)	10.0 (0.0 to 130.0)
Missing	372	353	725
n	214	215	429
***Microinvasion* (n, %)**			
Present	18 (3.1)	22 (3.9)	40 (3.5)
Not present	233 (39.8)	217 (38.2)	450 (39.0)
Possible	47 (8.0)	54 (9.5)	101 (8.8)
Missing	288 (49.1)	275 (48.4)	563 (48.8)
***Margins clear of tumour (CIS)* (n, %)**			
Reaches margin	94 (16.0)	83 (14.6)	177 (15.3)
Uncertain	19 (3.2)	18 (3.2)	37 (3.2)
Does not reach margin	333 (56.8)	347 (61.1)	680 (58.9)
Missing	140 (23.9)	120 (21.1)	260 (22.5)
Distance of nearest margin to tumour (mm) (CIS)			
Mean (SD)	4.55 (4.88)	4.36 (5.05)	4.46 (4.96)
Median (range)	3.0 (0.0 to 40.0)	3.0 (0.0 to 50.0)	3.0 (0.0 to 50.0)
Missing	206	193	399
n	380	375	755
***Pure DCIS* (n, %)**			
Yes	43 (5.3)	48 (5.9)	91 (5.6)
No	749 (91.8)	728 (90.2)	1477 (91.0)
Missing	24 (2.9)	31 (3.8)	55 (3.4)

TABLE 7 *Pathology: in situ disease (continued)*

	MR scan	No MR scan	Total
Margins clear of tumour (pure DCIS) (n, %)			
Reaches margin	17 (39.5)	12 (25.0)	29 (31.9)
Uncertain	2 (4.7)	0 (0.0)	2 (2.2)
Does not reach margin	24 (55.8)	35 (72.9)	59 (64.8)
Missing	0 (0.0)	1 (2.1)	1 (1.1)
Distance of nearest margin to tumour (mm) (pure DCIS)			
Mean (SD)	4.98 (5.91)	3.52 (3.69)	4.24 (4.94)
Median (range)	3.5 (0.0 to 25.0)	2.0 (0.0 to 15.0)	3.0 (0.0 to 25.0)
Missing	3	7	10
n	40	41	81

TABLE 8 *Pathology: invasive disease*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
Invasive disease (n, %)			
Yes	743 (91.1)	723 (89.6)	1466 (90.3)
No	48 (5.9)	53 (6.6)	101 (6.2)
Missing	25 (3.1)	31 (3.8)	56 (3.5)
Pathology (n, %)			
Mucinous carcinoma	20 (2.7)	13 (1.8)	33 (2.3)
Tubular carcinoma	24 (3.2)	28 (3.9)	52 (3.5)
Ductal NST	570 (76.7)	544 (75.2)	1114 (76.0)
Lobular carcinoma	63 (8.5)	70 (9.7)	133 (9.1)
Not assessable	2 (0.3)	1 (0.1)	3 (0.2)
Mixed	8 (1.1)	15 (2.1)	23 (1.6)
Other	54 (7.3)	52 (7.2)	106 (7.2)
Missing	2 (0.3)	0 (0.0)	2 (0.1)
Grade (n, %)			
I	177 (23.8)	179 (24.8)	356 (24.3)
II	358 (48.2)	331 (45.8)	689 (47.0)
III	200 (26.9)	205 (28.4)	405 (27.6)
Missing	8 (1.1)	8 (1.1)	16 (1.1)

continued

TABLE 8 *Pathology: invasive disease (continued)*

	MR scan	No MR scan	Total
Extent of disease (n, %)			
Localised	613 (82.5)	631 (87.3)	1244 (84.9)
Multifocal	90 (12.1)	72 (10.0)	162 (11.1)
Not assessable	11 (1.5)	5 (0.7)	16 (1.1)
Multicentric	11 (1.5)	6 (0.8)	17 (1.2)
Missing data	18 (2.4)	9 (1.2)	27 (1.8)
Size of index lesion (mm)			
Mean (SD)	17.23 (9.50)	17.43 (9.98)	17.33 (9.74)
Median (range)	15.0 (1.7 to 98.0)	15.0 (0.3 to 115.0)	15.0 (0.3 to 115.0)
Missing	12	11	23
n	731	712	1443
Size of invasive tumour and DCIS (mm)			
Mean (SD)	21.83 (14.25)	20.74 (12.21)	21.29 (13.28)
Median (range)	18.0 (3.0 to 130.0)	18.0 (1.5 to 115.0)	18.0 (1.5 to 130.0)
Missing	127	112	239
n	616	611	1227
Margins clear of tumour (invasive) (n, %)			
Reaches margin	99 (13.3)	106 (14.7)	205 (14.0)
Uncertain	17 (2.3)	26 (3.6)	43 (2.9)
Does not reach margin	620 (83.4)	582 (80.5)	1202 (82.0)
Missing	7 (0.9)	9 (1.2)	16 (1.1)
Distance of nearest margin to tumour (mm)			
Mean (SD)	4.57 (4.22)	4.51 (4.67)	4.54 (4.44)
Median (range)	4.0 (0.0 to 40.0)	4.0 (0.0 to 50.0)	4.0 (0.0 to 50.0)
Missing	53	57	110
n	690	666	1356

Intention-to-treat population

Table 9 summarises the analysis of the reoperation rate. Overall, 309 patients (19.0%) underwent a repeat operation or mastectomy at further operation, within 6 months of randomisation, or a pathologically avoidable mastectomy at initial operation [MRI: 153 (18.8%); no MRI: 156 (19.3%)]. The difference between the groups was compared using a chi-squared test, and is small at just 0.58% (95% CI –3.24 to 4.40). The difference between the arms is not significant at the 5% significance level [test statistic = 0.09, degrees of freedom (df) = 1, $p = 0.7657$]. The reoperation rates are high in comparison with the rates anticipated when the sample size calculation was carried out, and are almost double the quality assurance standard for the NHS BSP,[65] which is < 10% reoperation rate for incomplete tumour excision. The median time from randomisation to further surgery was 41 days (range 13–170), and was similar between the arms.

Multivariate analysis adjusting for the minimisation factors only was also carried out and results are displayed in *Table 10*. The addition of MRI to conventional triple assessment was not found to be a statistically significant factor associated with reoperation rate [odds ratio (OR) 0.96, 95% CI 0.75 to 1.24, $p = 0.7691$]. An OR of less than one indicates reduced reoperation rate for patients undergoing an MR scan; however, the CI is very tight around one, indicating no significant

difference. Considering the minimisation factors, neither breast density nor surgeon were found to be statistically significantly associated with reoperation rates ($p = 0.5101$ and $p = 0.3391$, respectively). Age, however, was found to be statistically significant (OR 0.64, 95% CI 0.47 to 0.86, $p = 0.0029$), indicating that patients aged 50 or over are less likely to undergo a repeat operation than patients aged under 50. Similar results were found when adjusting for the additional factors menopausal status and use of medical contraception or HRT, with the exception that age was no longer found to be statistically significantly associated with reoperation rate.

Type of reoperation is displayed in *Table 11*. In total, 175 patients (10.8%) underwent a further WLE and 109 patients (6.7%) underwent a mastectomy at further operation. Other operations were subcutaneous mastectomy and reconstruction, and subcutaneous mastectomy and lateral dorsal flap reconstruction. Twenty-three patients (1.4%) underwent a pathologically avoidable mastectomy [18 patients (MRI: 16; no MRI: 2)] or a mastectomy by choice [five patients (MRI: 3; no MRI: 2)] at initial operation [MRI: 19 (2.3%); no MRI: 4 (0.5%)]. Those patients with missing data regarding further surgery were classed as being lost to follow-up.

Per-protocol population

In the per-protocol population, 142 (18.91%) patients in the MRI group underwent a reoperation, compared with 159 (19.23%) in the no-MRI group. As for the ITT population, univariate analysis was carried out using a chi-squared test, as was multivariate analysis using logistic regression. There was no statistically significant difference in the reoperation rates between the two groups.

Sensitivity analysis

A sensitivity analysis was conducted to assess the effect on the primary ITT results of including patients recruited to a centre where a higher than average number of patients did not receive the intervention to which they were randomised. This patient population excluded 48 patients recruited to this centre. No statistically significant difference in reoperation rate was identified between patients receiving MRI and those receiving triple assessment alone under univariate analysis (MRI: 18.79%, no MRI: 19.57%, difference 0.78%, 95% CI –3.11 to 4.66, $p = 0.6958$), or under multivariate analysis.

The per-protocol analysis and sensitivity analysis results are consistent with the ITT results and confirm that there were no statistically significant differences between the MRI and no MRI groups

TABLE 9 *Primary end point: reoperation rate (univariate analysis)*

	MRI (*n*, %)	No MRI (*n*, %)	Difference (%) (no MRI–MRI), 95% CI	df	Test statistic	*p*-value
ITT	153/816 (18.75)	156/807 (19.33)	0.58 (–3.24 to 4.40)	1	0.09	0.7657
Per-protocol	142/751 (18.91)	159/827 (19.23)	0.32 (–3.56 to 4.20)	1	0.03	0.8724

TABLE 10 *Primary analysis: reoperation rate (multivariate analysis, ITT population)*

	Estimate	Standard error	OR	95% CI	Wald test statistic	*p*-value
Allocation: MRI vs no MRI	–0.04	0.13	0.96	(0.75 to 1.24)	0.09	0.7691
Age: ≥ 50 vs < 50	–0.45	0.15	0.64	(0.47 to 0.86)	8.88	0.0029
BI-RADS: 2, 3, 4 vs 1	0.14	0.21	1.15	(0.76 to 1.73)	0.43	0.5101
Surgeon: individual surgeons recruiting ≥ 10 patients vs all surgeons recruiting < 10 patients					50.44	0.3391

TABLE 11 *Primary end point: type of reoperation (ITT population)*

	MR scan, *n* (%)	No MR scan, *n* (%)	Total, *n* (%)
Repeat operations within 6 months			
Further WLE	85 (10.4)	90 (11.2)	175 (10.8)
Mastectomy	48 (5.9)	61 (7.6)	109 (6.7)
Other	1 (0.1)	1 (0.1)	2 (0.1)
Contralateral breast operation only – not a repeat operation	1 (0.1)	0 (0.0)	1 (0.1)
Pathologically avoidable initial mastectomy/ patient choice	19 (2.3)	4 (0.5)	23 (1.4)
Did not undergo further surgery	658 (80.6)	645 (79.9)	1303 (80.3)
Lost to follow-up	4 (0.5)	6 (0.7)	10 (0.6)
Total	816 (100.0)	807 (100.0)	1623 (100.0)

in the proportions of patients undergoing a repeat operation or mastectomy at further operation, or a pathologically 'avoidable' mastectomy at initial operation. Since there were no differences between the results of the ITT analysis and the sensitivity and per-protocol analyses, all further analyses were conducted on the complete ITT population.

Ancillary analyses

Exploratory analysis was conducted to consider 'consultant surgeon' as a categorical variable, grouped as surgeons recruiting less than 10 patients versus surgeons recruiting 10–19 patients versus surgeons recruiting 20 or more patients. Although surgeon was not found to be statistically significantly associated with reoperation rates, a trend was shown towards reduced reoperation rates for surgeons recruiting at least 20 patients (OR 0.77, 95% CI 0.54 to 10.9).

The effect of the addition of MRI to conventional triple assessment on the reoperation rate for those patients who were recruited by surgeons recruiting at least the median number of patients (7, range 1–119) was also considered, as well as for those patients recruited by surgeons who had a reoperation rate of less than 10% (as this is the quality assurance standard for the NHS BSP), as exploratory additional analyses.

When considering only those patients recruited by surgeons recruiting at least the median number of patients, 1447 patients were included in the analysis. The proportion of patients undergoing a reoperation in this population in the MRI arm was 18.2% and in the no-MRI arm it was 18.8%. The addition of MRI to conventional triple assessment was not statistically significantly associated with the reoperation rate within 6 months under multivariate analyses (OR 0.95, 95% CI 0.73 to 1.25, $p = 0.7335$).

Given the NHS BSP quality assurance standard of a reoperation rate of less than 10%, we wanted to consider the effect of MRI on the reoperation rate for those patients recruited by surgeons with a low reoperation rate. The median reoperation rate per surgeon was 20.0% (range 0–100%). Considering only those patients recruited by surgeons with a reoperation rate of less than 10%, 313 patients were included in this exploratory analysis (recruited by 29 surgeons). The median number of patients recruited by these surgeons was four (range 1–119). The proportion of patients undergoing a reoperation in this population in the MRI arm was 5.0%, and in the no-MRI arm it was 5.9%. No statistically significant difference in reoperation rates due to the addition of MRI to conventional triple assessment was observed under multivariate analysis (OR 0.82, 95% CI 0.31 to 2.21, $p = 0.6979$).

As proposed in the statistical analysis plan, multilevel modelling was carried out on the primary end point to quantify the level of surgeon effect, considering the complete ITT population. A non-linear mixed model was fitted to the data considering treatment allocation, age and breast density as fixed categorical variables, and 'surgeon' was fitted as a random effect with all 107 levels. The results of the multilevel modelling analysis are displayed in *Table 12*; there is no statistically

significant surgeon effect on the reoperation rate (test statistic = 1.55, df = 106, $p = 0.1248$).

The primary end point considered reoperation rate within 6 months of randomisation; however, there were some patients who underwent a repeat operation or mastectomy at further surgery outside the 6 months' time frame. Since there were only 14/1623 patients (0.9%) [MRI: 6 (0.7%); no MRI: 8 (1.0%)] who underwent a repeat operation/mastectomy at further surgery outside the 6 months, sensitivity analyses were not conducted to incorporate these patients.

As there were less than 1% of patients lost to follow-up, a preplanned sensitivity analysis was not conducted to class these patients as having a reoperation. Similarly, since less than 1% of patients underwent a mastectomy at initial operation that was due to patient decision, a pre-planned sensitivity analysis was not conducted to class these patients as not having a reoperation.

Subgroup analyses

Prespecified exploratory analyses were conducted to assess the interactive effect of breast density, menopausal status, tumour type and tumour grade, on the effectiveness of triple assessment combined with MRI compared with no MRI. Tumour type was classed as lobular carcinoma versus all other types, and included patients with invasive carcinoma only, and breast density was categorised as ACR BI-RADS group 1 or 2 versus ACR BI-RADS group 3 or 4, and is taken from the mammography form. Overall, 316/1623 patients (19.5%) had missing data for breast density, menopausal status, tumour type or tumour grade, therefore this exploratory analysis was carried out on 1307 patients. None of the interactions was found to be statistically significant at the 5% significance level; however, tumour type was identified as a statistically significant variable associated with reoperation rate (test statistic = 7.20, $p = 0.0073$). Due to the large amount of patients with missing data, however, these results are interpreted with caution.

In total, 133/1466 (9.1%) patients with invasive carcinoma had lobular carcinoma (MRI: 8.5%; no MRI: 9.7%). Prespecified exploratory analyses were conducted to identify any interactive effect of lobular carcinoma on the effectiveness of MRI compared with no MRI. A complete case analysis was conducted; therefore, patients for whom we could not identify whether they had lobular carcinoma were excluded from the analyses, leaving an exploratory analysis population of 1556 patients. Patients with DCIS alone were included in the analysis and classed as not having lobular carcinoma. Multivariate analysis was carried out to incorporate an interaction term between randomised allocation and whether or not a patient had lobular carcinoma. Although the interaction term was not found to be statistically significant, patients with lobular carcinoma were statistically significantly more likely to undergo a reoperation (OR 0.52, 95% CI 0.30 to 0.92, test statistic = 5.08, $p = 0.0242$) at the 5% significance level, compared with patients who did not have lobular carcinoma. However, results are again interpreted with caution due to the low number of patients with lobular carcinoma.

The correlation between the size of the index lesion via the imaging methods and via histopathology was also considered according to whether or not patients with invasive carcinoma had lobular carcinoma. Pearson correlation coefficients for patients with lobular carcinoma are: mammography = 0.37; USS = 0.29; MRI = 0.40. Corresponding Pearson correlation coefficients for patients without lobular carcinoma are: mammography = 0.49; USS = 0.49; MRI = 0.53. Correlation for patients with lobular carcinoma was weaker than for those patients without lobular

TABLE 12 *Primary end point: multilevel modelling*

	Estimate	Standard error	df	Test statistic	*p*-value
Intercept	–1.15	0.24	106	–4.79	< 0.0001
Allocation: MRI vs No MRI	–0.03	0.13	106	–0.26	0.7944
Age: ≥ 50 vs < 50	–0.51	0.15	106	–3.54	0.0006
BI-RADS: 2, 3, 4 vs 1	0.12	0.20	106	0.59	0.5597
Surgeon random effect: variance	0.08	0.05	106	1.55	0.1248

carcinoma; however, the number of patients with lobular carcinoma is small, as previously noted.

Finally, reoperation rates according to treatment arm were compared for patients with lobular carcinoma. There was no significant difference in the reoperation between the two trial arms, for patients with lobular carcinoma, with confidence intervals for the difference (OR) being wide and spanning zero (one for the OR) (MRI: 25.40%, no MRI: 30.99%, difference 5.59%, 95% CI –9.62 to 20.80, $p = 0.4737$; OR 0.76, 95% CI 0.36 to 1.62). Corresponding reoperation rates for patients who did not have lobular carcinoma were: MRI: 18.03%, no MRI: 18.40%, difference 0.37%, 95% CI –3.64 to 4.38.

The majority of patients recruited to the COMICE trial were over the age of 50. Multivariate analysis of the primary end point identified age to be a significant factor, with patients under the age of 50 more likely to undergo a reoperation than patients over 50. Additional ad hoc exploratory analyses were therefore conducted on these subgroups of patients. Multivariate analysis adjusting for the stratification factors and incorporating an interaction term between age and MRI was carried out. No statistically significant interaction between age and MRI was found (test statistic = 0.16, $p = 0.6915$).

Secondary end points

Analysis of factors associated with differences in imaging findings

The analysis of factors associated with differences in imaging findings (in terms of size of lesion and extent of disease) and histopathology, which may influence referral for MRI, was conducted for patients with complete data for each of the potential risk factors included in the analyses. Analyses were conducted on patients with CIS alone and on those with invasive disease both with and without coexisting CIS. When including CIS alone patients, tumour grade was categorised as grade I, II, III or CIS alone. Forwards stepwise linear (logistic) regression was carried out when considering factors associated with differences in findings in size of lesion (extent of disease).

The final model for differences in size of lesion between MRI and pathology included ER status only ($n = 685$, test statistic = 6.16, df = 2, $p = 0.0458$), and the overall r^2-value was just 0.01, indicating that the model does little to explain the variance of the data. When the analysis was conducted excluding patients for whom tumour type was DCIS alone, the final model included ER status (test statistic = 7.64, df = 2, $p = 0.0219$) and menopausal status (test statistic = 5.15, df = 1, $p = 0.0233$), ($r^2 = 0.02$). These results indicate that patients who are ER positive tend to have MRI results closer to the results of pathology, and that the MRI identifies larger lesions than pathology for post-menopausal women.

The final model for differences in extent of disease between MRI and pathology ($n = 676$) included age (test statistic = 9.34, df = 1, $p = 0.0022$) and tumour type (test statistic = 21.55, df = 7, $p = 0.0030$), ($r^2 = 0.04$), indicating that MRI is more likely to agree with histopathology for patients who are over 50 and have ductal NST tumours. When the analysis was conducted excluding patients for whom tumour type was CIS alone, the final model included the same variables.

The final model for differences in size of lesion between mammography and histopathology ($n = 1396$) included tumour type (test statistic = 55.5, df = 7, $p = < 0.0001$), menopausal status (test statistic = 21.57, df = 1, $p = <0.001$) and nodal status (test statistic = 19.19, df = 2, $p = < 0.0001$), ($r^2 = 0.06$), indicating that mammography identifies size of lesion closer to that identified via histopathology for patients with ductal NST tumours and who are post-menopausal, and that patients who are node positive tend to have smaller lesions identified via mammography than histopathology. When the analysis was repeated excluding those patients with CIS alone, the final model included the same variables.

The final model for differences in extent of disease between mammography and histopathology ($n = 1326$) included age (test statistic = 28.01, df = 1, $p = < 0.0001$), breast density (test statistic = 11.63, df = 1, $p = 0.0006$), tumour type (test statistic = 23.20, df = 7, $p = 0.0016$) and nodal status (test statistic=7.05, df=2, p = 0.0295), (r^2=0.06), indicating that mammography is more likely to agree with the histopathology for patients who are over 50, have BI-RADS group 1, have CIS only or ductal NST, and who are node negative. When the analysis was repeated excluding those patients with CIS alone, the final model included the same variables.

The final model for differences in size of lesion between USS and histopathology ($n = 1447$) included tumour type (test statistic = 84.57, df = 7, $p = <0.0001$) and nodal status (test statistic = 20.01, df = 2, p = < 0.0001) ($r^2 = 0.10$), indicating that patients who have ductal NST tumours and who are node negative are more likely to have similar size on USS measurements and histopathology. When the analysis was repeated excluding those patients with CIS alone, the final model included the same variables.

The final model for differences in extent of disease between USS and histopathology ($n = 1433$) included tumour type (test statistic = 17.02, df = 7, $p = 0.0173$) and nodal status (test statistic = 43.50, df = 2, $p = < 0.0001$), ($r^2 = 0.10$), indicating that USS is more likely to agree with histopathology for patients who have ductal NST tumours and who are node negative. When the analysis was repeated excluding those patients with CIS alone, the final model included the same variables.

Summaries of discrepancies in size of lesion between mammography and USS are displayed in *Table 13*. If size of index lesion (mammography) is missing and size of index lesion (USS) is not, then the method that identifies the largest tumour diameter was taken to be USS (and vice versa). For six patients for whom both methods identify the largest tumour diameter, extent of disease was different for the two methods. Model building for the factors associated with differences in size of index lesion, and extent of disease, between mammography or USS and histopathology using the method that identifies the largest tumour diameter excludes these patients.

The final model for differences in size of index lesion between histopathology and either mammography or USS, according to which method identified the largest tumour diameter ($n = 1463$) included tumour type (test statistic = 66.22, df = 7, $p = < 0.0001$), menopausal status (test statistic = 6.82, df = 1, $p = 0.0090$) and nodal status (test statistic = 15.51, df = 2, $p = 0.0004$), ($r^2 = 0.06$), indicating that the imaging method is more likely to reflect the size of lesion identified via histopathology for patients with ductal NST tumours and patients who are node negative, and that post-menopausal patients are more likely to have larger lesions identified via imaging than via histopathology. When the analysis was repeated excluding those patients with CIS alone, the final model included the same variables as above.

The final model for differences in extent of disease between histopathology and either mammography or USS, according to which method identifies the largest tumour diameter, ($n = 1444$) included age (test statistic = 6.24, df = 1, $p = 0.0125$), tumour type (test statistic = 16.02, df = 7, $p = 0.0249$), nodal status (test statistic = 18.87, df = 2, $p = < 0.0001$) and PR status (test statistic = 8.38, df = 2, $p = 0.0151$), ($r^2 = 0.03$), indicating that the imaging methods are more likely to agree with histopathology for patients who are over 50, have ductal NST tumours and are node negative. When the analysis was repeated excluding those patients with CIS alone, the final model included the same variables as above with the exception of PR status.

A summary of the imaging modality that showed the smallest discrepancy in size, compared to histopathology, is displayed in *Table 14*, considering only those patients randomised to receive MRI. For some patients, more than one method gave the smallest size therefore the summary is not mutually exclusive. The proportion of patients for whom each method identified the smallest discrepancy is similar for each of the imaging methods.

There was medium correlation between the size of index lesion identified via each of the imaging methods and via histopathology, with the Pearson correlation coefficient ranging from 0.42 (USS) to 0.51 (MRI). Correlation between size of index lesion identified on each of the imaging methods and size of DCIS on pathology, for patients with DCIS alone, was very weak, with Pearson correlation coefficients ranging from 0.18 (USS) to just 0.34 (mammography); however, there are very few patients with DCIS alone. The correlation between the size of the index lesion on each of the imaging methods and the size of the invasive lesion + DCIS on pathology is, however, only slightly stronger with Pearson correlation coefficients ranging from 0.35 to 0.38. Correlation is strongest when considering the size of invasive carcinoma for those patients with invasive carcinoma alone, with Pearson correlation coefficients ranging from 0.46 for MRI to 0.61 for mammography.

Radiologist effect

Multilevel modelling was carried out on the final model identified for factors associated with differences in findings between MRI and histopathology, to investigate whether there was a radiologist effect. Results identified that there is a

TABLE 13 *Factors associated with differences in findings: discrepancies between mammography and USS*

Discrepancy in size between mammography and USS (USS – mammography)	
Mean (SD)	–2.2 (9.2)
Median (range)	–2.0 (–80.0 to 84.0)
Missing	140
n	1483
Method that identifies the largest tumour diameter *(n, %)*	
Mammography	950 (58.5)
USS	412 (25.4)
Both	230 (14.2)
Missing data	31 (1.9)

statistically significant radiologist effect, associated with differences in size of lesion between MRI and histopathology (covariance estimate = 15.84, 95% CI 7.41 to 54.35, test statistic = 2.08, $p = 0.0186$); however, the residual parameter estimate of 94.23 indicates that most of the variation in data is due to differences in variables at the patient level, not radiologists. No radiologist effect was found to be associated with differences in extent of disease.

Effectiveness of imaging

Agreement of histopathology results with imaging findings in terms of patient management was considered for patients randomised to receive an MR scan, as previously outlined. According to histopathology findings, WLE should have been the planned management for 1136/1623 patients (70.0%) [MRI: 561 (68.8%); no MRI: 575 (71.3%)], and mastectomy should have been the planned management for 377/1623 patients (23.2%) [MRI: 196 (24.0%); no MRI: 181 (22.4%)]. Planned management was not determinable for 110 patients (6.8%) [MRI: 59 (7.2%); no MRI: 51 (6.3%)]. Extent of disease and size of index lesion according to histopathology is summarised in *Table 15*, for the 1513 patients with determinable patient management according to histopathology. Patients with DCIS alone were classed as having localised disease. Patients for whom extent of disease was missing or not assessable but for whom size of index lesion was ≥ 30 mm were included in this analysis, as these patients should have undergone a mastectomy due to the size of their lesion according to the definition given previously.

Of the 757 patients in the MRI arm with patient management determinable according to histopathology, there were 66 patients whose management according to MRI could not be determined; therefore the effectiveness of imaging analysis was carried out on 691 patients. The number of true-positive, true-negative, false-positive and false-negative cases for patients randomised to receive an MR scan is displayed in *Table 16*.

There were 458 true-negative cases, i.e. MRI correctly identified WLE for 458/547 patients (83.7%), and 89/547 false-negative cases, i.e. MRI identified WLE for 89 patients (16.3%) when histopathology findings indicated the patient should have undergone a mastectomy. The corresponding sensitivity, specificity, positive predictive and negative predictive values are displayed in *Table 17*, with corresponding 95% CIs.

Sensitivity, specificity and positive and negative predictive values for mammography and/or USS were not calculated as the trial was designed to only recruit patients who were scheduled for a WLE, based on the results of triple assessment alone.

Patient management as determined by histopathology is summarised in *Table 18*, according to patients' actual management (i.e. as determined from the surgery form), and includes all 1623 patients. Since patients undergoing triple assessment alone should have undergone a WLE based on these results, we concentrate on the proportion of patients that correctly underwent a WLE, according to histopathology results. In this case, 544 of the 751 patients (72.4%) in the MRI arm who underwent a WLE did so correctly, according to histopathology; however, 15 of the 58 patients (25.9%) in the MRI arm who underwent

TABLE 14 *Factors associated with differences in findings: discrepancy in size compared with histopathology. Method that shows the smallest discrepancy in size compared with histopathology (not mutually exclusive) (total n = 816)*

	***n* (%)**
Mammography	303 (37.1)
USS	315 (38.6)
MRI	328 (40.2)
Missing data	55 (6.7)

a mastectomy, did so incorrectly according to histopathology results. For patients randomised to no MRI, 569 of the 787 patients (72.3%) who underwent a WLE did so correctly. Also, 152 of the 751 patients in the MRI arm (20.2%) undergoing a WLE did so incorrectly according to histopathology (i.e. they should have undergone a mastectomy). Results for patients in the no-MRI arm are similar, with 175 of the 787 patients (22.2%) undergoing WLE doing so incorrectly according to histopathology.

Diagnostics comparing the number of malignant lesions identified via histopathology and via MRI were also calculated and are displayed in *Table 19*, with corresponding sensitivity, specificity, positive and negative predictive values displayed in *Table 20*, with 95% CIs.

In order to address any indirect evidence of false–negative pathology, the recurrence data in the histopathology/MRI discrepant groups (patients for whom patient management determined via MRI results was WLE, but patient management determined via histopathology was mastectomy or vice versa) were examined. The number of patients experiencing a local recurrence within one and three years of randomisation was low (one and 22 patients respectively) and no evidence of in-direct false negative pathology was identified.

TABLE 15 *Effectiveness of imaging: extent of disease and size of index lesion*

	MR scan (*n* = 757), *n* (%)	**No MR scan (*n* = 756), *n* (%)**	**Total (*n* = 1513), *n* (%)**
Extent of disease (histopathology)			
Localised	650 (85.9)	676 (89.4)	1326 (87.6)
Multifocal	90 (11.9)	72 (9.5)	162 (10.7)
Multicentric	11 (1.5)	6 (0.8)	17 (1.1)
Not assessable	2 (0.3)	1 (0.1)	3 (0.2)
Missing data	4 (0.5)	1 (0.1)	5 (0.3)
Size of index lesion/invasive and DCIS/CIS only			
< 30 mm	627 (82.8)	621 (82.1)	1248 (82.5)
≥ 30 mm	129 (17.0)	133 (17.6)	262 (17.3)
Missing data	1 (0.1)	2 (0.3)	3 (0.2)
Histopathology			
Localised < 30 mm	561 (74.1)	575 (76.1)	1136 (75.1)
Localised ≥ 30 mm	89 (11.8)	101 (13.4)	190 (12.6)
Multifocal/multicentric	101 (13.3)	78 (10.3)	179 (11.8)
≥ 30 mm, but extent of disease missing or not assessable	6 (0.8)	2 (0.3)	8 (0.5)

TABLE 16 *Effectiveness of imaging: diagnostics of patients randomised to receive MRI*

		Histopathology		
		WLE	**Mastectomy**	**Total**
MRI	**WLE**	458 (true negative)	89 (false negative)	547
	Mastectomy	55 (false positive)	89 (true positive)	144
	Total	513	178	691

Further additional exploratory analyses were conducted to consider the level of agreement in size of tumour between histopathology (the gold standard) and each of the imaging methods, according to tumour stage, considering the size of index lesion alone, and size of index lesion plus the size of DCIS, for patients with invasive carcinoma. Summaries were based on all patients with complete data (i.e. size of lesion on imaging method and size of lesion on pathology), and percentages were calculated as number of patients with imaging stage *x* divided by the total number of patients with pathology stage *x*, i.e. pathology staging is taken to be the gold standard. Weighted kappa statistics were calculated with corresponding 95% CIs as a measure of association between the imaging method in question and pathology. Based on criteria originally proposed by Landis and Koch, kappa values greater than 0.75 are often taken as representing excellent agreement; values between 0.4 and 0.75 as fair to good agreement; and values less than 0.4 as moderate or poor agreement.[74] Weighted statistics were used to incorporate partial agreement (e.g. between adjacent cells). A detailed table of agreement between the imaging methods and pathology for patients with invasive carcinoma, considering the size of index lesion only, is displayed in Appendix 15, *Table 46*). Weighted kappa statistics indicate that agreement between all imaging methods and pathology is borderline moderate to fair. In general, the imaging methods tend to upstage smaller tumours (i.e. T1a to T1c) and downstage larger tumours (T2 and T3), but it should be noted that COMICE recruited patients were scheduled for a WLE as per triple assessment alone, and therefore these results may not be a good representation of how the imaging methods perform in higher-staged tumours.

TABLE 17 *Effectiveness of imaging: sensitivity, specificity, positive predictive and negative predictive values*

	Value	**Approximate 95% CI**
Sensitivity	50.0	42.65 to 57.35
Specificity	89.3	86.60 to 91.96
Positive predictive value	61.8	53.87 to 69.74
Negative predictive value	83.7	80.64 to 86.82

Agreement between the imaging methods and pathology for patients with invasive carcinoma, considering the size of the invasive lesion plus DCIS, is also displayed in Appendix 15, *Table 46*. Agreement between the imaging methods and pathology is slightly lower for mammography and USS when incorporating size of DCIS than agreement when just considering the size of the index lesion. Agreement between MRI and pathology is similar when considering either index lesion only or invasive + DCIS, and agreement remains borderline moderate to fair.

The level of agreement in size of tumour between histopathology and each of the imaging methods to within ± 5mm was also considered, and results are displayed in *Table 21*. Results are displayed for patients with invasive carcinoma considering both index lesion only and invasive + DCIS. All methods perform equally well when considering size of index lesion only, with between 69.5% and 72.4% of patients having agreement for each of the methods. When we then incorporate DCIS, it can be seen that agreement according to USS is lower (61.2%) than for either MRI (66.4%) or mammography (65.8%), again reflecting that USS may not be very good at identifying DCIS.

TABLE 18 *Effectiveness of imaging: patient management according to histopathology versus actual patient management*

	Actual patient management						
	WLE (*n* = 1538)	**Mastectomy (*n* = 68)**	**Other (*n* = 2)**	**No surgery (*n* = 4)**	**Lost to follow-up (*n* = 2)**	**Missing data (*n* = 9)**	**Total (*n* = 1623)**
***All patients: patient management determined via histopathology* (n, %)**							
Missing data	98 (6.4)	1 (1.5)	0 (0.0)	4 (100.0)	2 (100.0)	5 (55.6)	110 (6.8)
WLE	1113 (72.4)	18 (26.5)	2 (100.0)	0 (0.0)	0 (0.0)	3 (33.3)	1136 (70.0)
Mastectomy	327 (21.3)	49 (72.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	377 (23.2)
	WLE (*n* = 751)	**Mastectomy (*n* = 58)**	**Other (*n* = 2)**	**No surgery (*n* = 2)**	**Lost to follow-up (*n* = 1)**	**Missing data (*n* = 2)**	**Total (*n* = 816)**
***MRI: patient management determined via histopathology* (n, %)**							
Missing data	55 (7.3)	0 (0.0)	0 (0.0)	2 (100.0)	1 (100.0)	1 (50.0)	59 (7.2)
WLE	544 (72.4)	15 (25.9)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	561 (68.8)
Mastectomy	152 (20.2)	43 (74.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	196 (24.0)
	WLE (*n* = 787)	**Mastectomy (*n* = 10)**	**Other (*n* = 0)**	**No surgery (*n* = 2)**	**Lost to follow-up (*n* = 1)**	**Missing data (*n* = 7)**	**Total (*n* = 807)**
***No MRI: patient management determined via histopathology* (n, %)**							
Missing data	43 (5.5)	1 (10.0)	0 (0.0)	2 (100.0)	1 (100.0)	4 (57.1)	51 (6.3)
WLE	569 (72.3)	3 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)	575 (71.3)
Mastectomy	175 (22.2)	6 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	181 (22.4)

TABLE 19 *Effectiveness of imaging: diagnostics of patients randomised to receive MRI, considering the number of lesions identified*

		Histopathology		
		1	**≥2**	**Total**
MRI	**1**	503 (true negative)	49 (false negative)	552
	≥2	39 (false positive)	39 (true positive)	78
	Total	542	88	630

TABLE 20 *Effectiveness of imaging: sensitivity, specificity, positive predictive and negative predictive values, considering the number of lesions identified*

	Value	**Approximate 95% CI**
Sensitivity	44.3	33.94 to 54.70
Specificity	92.8	90.63 to 94.98
Positive predictive value	50.0	38.90 to 61.10
Negative predictive value	91.1	88.75 to 93.50

Change in clinical management

A change in clinical management due to MRI results (i.e. not due to patient choice) was proposed for 55/816 patients (6.7%). There were four patients for whom a WLE was not the proposed clinical management; however, this was due to patient decision only and therefore these patients were not classed as having a change in management due to MRI results. The proposed clinical management (due to MRI results or patient choice) was conversion to mastectomy for 55 patients (6.7%); conversion to primary chemotherapy for one patient (0.1%); WLE and a reduction mammoplasty for one patient (0.1%); no surgery for one patient (0.1%); and for one patient the proposed change of clinical management was missing. Overall, 736 patients (90.2%) were scheduled for a WLE (including quadrantectomy and miniflap).

The reason for a proposed change in clinical management due to MRI results for 50/55 patients (90.9%) was that MRI findings indicated additional disease in the randomised breast. Of these patients, 14 (28.0%) underwent a pathologically avoidable mastectomy at initial operation. Four patients had other reasons for change in management, which were: review of mammography indicated calcification (one patient); review of mammography indicated DCIS near nipple (one patient); review of USS and core biopsy showed DCIS (one patient); and lung cancer treatment takes priority (one patient). The reason for change in management was missing for one patient.

Additional findings in the contralateral breast (regardless of malignancy) were identified for 62 patients (7.6%) via MRI. Of these 62 patients, 57 (91.9%) had one lesion identified, and five (8.1%) had two lesions identified. The planned procedure to the contralateral breast was WLE for 12/62 patients (19.4%) and mastectomy for 1/62 patient (1.6%); 17/62 patients had other planned management for the contralateral breast, which were repeat MRI (14 patients), open diagnostic biopsy (one patient) and no planned procedure (two patients). Planned management of the contralateral breast was missing for 32/62 patients (51.7%).

TABLE 21 *Effectiveness of imaging: agreement within ±5mm*

	MRI, *n* (%)	Mammography, *n* (%)	USS, *n* (%)
Index lesion only			
Yes	383 (69.5)	757 (72.4)	784 (71.5)
No	168 (30.5)	289 (27.6)	312 (28.5)
Invasive + DCIS			
Yes	342 (66.4)	658 (65.8)	639 (61.2)
No	173 (33.6)	342 (34.2)	405 (38.8)

Chemotherapy, radiotherapy and additional adjuvant therapies

As detailed in the previous chapter, patients with missing data regarding chemotherapy, radiotherapy or additional adjuvant therapy interventions were classed as having received chemotherapy, radiotherapy or additional adjuvant therapy, as appropriate, within 6 months of initial surgery. As data was missing for a relatively small number of patients, and was similar between the two arms, sensitivity analyses were not conducted to class these patients as not receiving the corresponding therapy.

Chemotherapy interventions

In total, chemotherapy data was missing for 9.2% of patients (MRI: 9.6%; no MRI: 8.8%), and 472 (29.1%) patients received chemotherapy within 6 months of initial surgery.

The chi-squared test without continuity correction was used to compare the proportion of patients receiving chemotherapy within 6 months of initial surgery (including those with missing data) between the study arms. In total, 321 patients (39.3%) randomised to receive MRI were classed as having received chemotherapy within 6 months of surgery, compared with 300 patients (37.2%) randomised to no MRI. The difference (no MRI – MRI) between the groups is small at –2.2% (95% CI –7.01 to 2.69), and is not significant at the 5% significance level (test statistic = 0.80, df = 1, $p = 0.3699$). A further 11 patients (1.3%) randomised to MRI received adjuvant chemotherapy although not within 6 months of surgery, compared with 11 patients (1.4%) randomised to no MRI.

Multivariate analysis adjusting for the minimisation factors was also carried out, using logistic regression. The addition of MRI to conventional triple assessment was not found to be a statistically significant factor associated with receiving chemotherapy within 6 months of surgery (OR

1.11, 95% CI 0.90 to 1.38, $p = 0.3135$). Age, however, was found to be statistically significant (OR 0.23, 95% CI 0.18 to 0.30, $p < 0.0001$), indicating that patients aged 50 or over are less likely to receive chemotherapy than patients aged less than 50.

Multivariate analysis was also carried out to incorporate other covariates that were identified as being prognostic of outcome (menopausal status, use of medical contraception and use of HRT). There were 24 patients who had missing data for these additional factors (MRI: 13; no MRI: 11) and were therefore not included in this analysis. Multivariate analysis incorporating additional factors was therefore carried out on a population of 1599 patients. In addition to age, use of medical contraception was found to be statistically significantly associated with receiving chemotherapy (OR 1.52, 95% CI 1.20 to 1.91, $p = 0.0004$), indicating that patients who have a history of using the contraceptive pill or slow-release injection are more likely to receive chemotherapy than patients who do not.

Summaries of time from surgery to starting chemotherapy for patients who received chemotherapy within 6 months of surgery, and summaries of chemotherapy treatment received can be found in Appendix 15. Patients can receive more than one type of chemotherapy. The time from surgery to receiving chemotherapy, and the proportion of patients receiving each type of chemotherapy is similar between the two arms.

Radiotherapy

In total, radiotherapy data was missing for 10.2% of patients (MRI: 10.2%; no MRI: 10.3%), and 940 (57.9%) patients received radiotherapy within 6 months of initial surgery.

The chi-squared test without continuity correction was used to compare the proportion of patients receiving radiotherapy within 6 months of initial surgery (including those patients with missing data) between the study arms. 553 patients (67.8%) randomised to receive MRI were classed as having received radiotherapy within 6 months of surgery, compared with 553 patients (68.5%) randomised to no MRI. The difference (no MRI – MRI) between the groups is small at 0.8% (95% CI –3.90 to 5.41), and is not significant at the 5% significance level (test statistic = 0.11, df = 1, $p = 0.7439$). A further 153 patients (18.8%) randomised to MRI received adjuvant radiotherapy although not within 6 months of surgery, compared with 157 patients (19.5%) randomised to no MRI.

Multivariate analysis adjusting for the minimisation factors was carried out, using logistic regression and the addition of MRI to conventional triple assessment was not found to be a statistically significant factor associated with receiving radiotherapy within 6 months of surgery (OR 0.96, 95% CI 0.78 to 1.19, $p = 0.7094$). Age, however, was found to be statistically significant (OR 2.34, 95% CI 1.84 to 2.98, $p < 0.0001$), indicating that patients aged 50 or over are more likely to receive radiotherapy than patients aged less than 50.

Multivariate analysis was also carried out to incorporate other covariates that were identified as being prognostic of outcome (menopausal status, use of medical contraception and use of HRT). In addition to age, menopausal status was also found to be statistically significant (OR 1.54, 95% CI 1.12 to 2.12, $p = 0.0087$), indicating that post-menopausal patients are more likely to receive radiotherapy than premenopausal patients, as reflected in the age variable.

Summaries of time from surgery to starting radiotherapy for patients who received radiotherapy within 6 months of surgery, and summaries of radiotherapy received can be found in Appendix 15. Patients can receive radiotherapy to more than one site. The median time from surgery to receiving radiotherapy for those receiving radiotherapy within 6 months was 2.8 months (range 0.7–6.0), and was similar between the two arms. The proportion of patients receiving radiotherapy to each site was also similar between the two arms.

Additional adjuvant therapies

In total, additional adjuvant therapy data was missing for 10.7% of patients (MRI: 11.6%; no MRI: 9.7%), and 833 (51.3%) patients received additional adjuvant therapies within 6 months of initial surgery.

The chi-squared test without continuity correction was used to compare the proportion of patients receiving additional adjuvant therapy, excluding chemotherapy and radiotherapy, within 6 months of initial surgery (including patients with missing data) between the study arms. Overall, 511 patients (62.6%) randomised to receive MRI were classed as

having received additional adjuvant therapy within 6 months of surgery, compared with 494 patients (61.2%) randomised to no MRI. The difference (no MRI – MRI) between the groups is small, at –1.4% (95% CI –6.26 to 3.44), and is not significant at the 5% significance level (test statistic = 0.34, df = 1, $p = 0.5591$). A further 129 patients (15.8%) randomised to MRI received additional adjuvant therapy, excluding chemotherapy and radiotherapy, although not within 6 months of surgery, compared with 153 patients (19.0%) randomised to no MRI.

Multivariate analysis adjusting for the minimisation factors was carried out, using logistic regression. The addition of MRI to conventional triple assessment was not found to be a statistically significant factor associated with receiving additional adjuvant therapy within 6 months of surgery (OR 1.07, 95% CI 0.87 to 1.31, $p = 0.5386$). Age, however, was found to be statistically significantly associated with receiving additional adjuvant therapy within 6 months (OR 1.90, 95% CI 1.47 to 2.45, $p < 0.0001$), indicating that patients aged 50 or over are more likely to receive additional adjuvant therapy than patients aged less than 50. This reflects the fact that women aged 50 or over are more likely to be ER positive and thus more likely to be able to receive hormone therapies.

Multivariate analysis was also carried out to incorporate other covariates that were identified as being prognostic of outcome (menopausal status, use of medical contraception and use of HRT). Menopausal status was found to be statistically significantly associated with receiving hormone therapy (OR 1.49, 95% CI 1.08 to 2.06, $p = 0.0139$), indicating that post-menopausal patients are more likely to receive additional adjuvant therapy than premenopausal patients. Age, however, was no longer statistically significant in this model, which is likely due to the strong association between age and menopausal status.

Summaries of time from surgery to receiving adjuvant therapy for patients who received adjuvant therapy within 6 months of surgery, and summaries of additional adjuvant therapies received can be found in Appendix 15. Patients can receive more than one type of adjuvant therapy. The median time from surgery to adjuvant therapy, for patients receiving adjuvant therapy within 6 months, was 0.9 months (range 0.0–6.0) and was similar between the two arms, as was the type of adjuvant therapies received.

Clinical significance of MRI-only-detected lesions

MRI-only-detected lesions < 5 mm

There were 25/816 patients (3.1%) randomised to receive an MRI scan, who had at least one additional lesion detected by MRI only, measuring less than 5 mm. This includes one patient whose lesion size was missing, for whom it was assumed the lesion measured < 5 mm. There were four patients with more than one < 5-mm MRI-only-detected lesion. The median size of the largest lesion was 4.0 mm (range 3.0–4.9).

Of these 25 patients, 14 (56.0%) received a repeat MR scan, three (12.0%) did not receive a repeat MR scan, and for eight patients (32.0%) we could not identify whether a repeat MR scan was undertaken, due to missing data. Two patients had a mastectomy therefore did not undergo a repeat MR scan and the reason for no repeat scan was missing for one patient. Details of repeat MRI findings are displayed in Appendix 15 (Clinical significance of < 5-mm MRI-only-detected lesions: repeat MRI findings) for those patients who underwent a repeat scan. Median time from randomisation to repeat MR scan was 15 months (range 8–19). Median time from starting adjuvant radiotherapy to repeat scan was 13 months (range 4–17) for the 12 patients who received radiotherapy. One patient had pulse sequences that were not successfully completed as although the local protocol was followed and all sequences attempted were successfully completed, the COMICE protocol was not performed.

Of those patients who did undergo a repeat scan, no-one had a clinically significant lesion evident. However, 11 patients (44.0%) did have missing data due to not undergoing a repeat MR scan or having a missing repeat MRI findings CRF; therefore, due to the problems associated with missing data, these results are inconclusive.

Of the 25 patients with < 5-mm MRI-only-detected lesions, only one patient (4.0%) had an unknown enhancing lesion evident on the repeat MR scan (size ≥ 5 mm, biopsy not performed, overall lesion score was 1).

≥ 5-mm biopsy-negative MRI-only-detected lesions

There were 66/816 patients (8.1%) randomised to receive an MRI scan who had at least one lesion detected by MRI only, which was biopsy negative (or, if biopsy was not performed, then whose overall lesion score was < 2) and measured at least 5 mm. This includes four patients for whom biopsy result

and/or lesion size was missing. It was assumed that these patients did have lesions that were negative and measured ≥ 5 mm. There were nine patients with more than one ≥ 5-mm MRI-only-detected lesion. The median size of the largest lesion was 8.0 mm (range 5.0–40.0 mm), and for patients who had more than one MRI-only-detected lesion the median size of the smallest lesion was 5.0 mm (range 5.0–15.0 mm).

Of the 66 patients with an MRI-detected biopsy negative lesion, 21 (31.8%) received a repeat MR scan, seven (10.6%) did not receive a repeat scan, and for 38 patients (57.6%) we could not identify whether a repeat MR scan was undertaken, due to missing data. The reasons for no scan were mastectomy (three patients), patient refusal (one patient), administrative error (one patient), lesion not thought to be suspicious (one patient) and lesion biopsied and confirmed benign, so the consultant felt there was no need for a repeat MR scan (one patient). Details of the repeat MRI findings are displayed in Appendix 15 (Clinical significance of ≥ 5-mm biopsy-negative MRI-only-detected lesions: repeat MRI findings) for those patients who underwent a repeat scan. Median time from randomisation to repeat MR scan was 15 months (range 8–29), and median time from starting adjuvant radiotherapy to repeat MR scan was 12 months (range 5–22) for the 15 patients who received radiotherapy. All 21 patients had all pulse sequences successfully completed.

The proportion of patients for whom a lesion was still evident at the repeat MR scan and was found to be clinically significant was 3/66 patients (4.5%); however, 45 patients (68.2%) had missing data due to not undergoing a repeat MR scan or having a missing repeat MRI findings CRF. Characteristics of the three clinically significant lesions were as follows:

- index lesion in contralateral breast at site 'upper half':
  - *initial scan* size = 6 mm, morphological impression 0, kinetic description 1, overall lesion score 1, biopsy negative, homogeneous enhancement, smooth margin, round in shape, proximity to: skin = 8 mm, chest wall = 70 mm, nipple retro-areolar complex (RAC) = 30 mm
  - *repeat scan* size = 9 mm, morphological impression 1, kinetic description 1, overall lesion score 2, biopsy not performed, homogeneous enhancement, smooth margin, oval in shape, proximity to: skin = 8 mm, chest wall = 39 mm, nipple RAC = 24 mm
- index lesion in contralateral breast at site 'left outer quadrant':
  - *initial scan* size = 7 mm, morphological impression 0, kinetic description 2, overall lesion score 2, biopsy negative, homogeneous enhancement, smooth margin, oval in shape, proximity to: skin = 16 mm, chest wall = 7 mm, nipple RAC = 78 mm
  - *repeat scan* size = 13 mm, morphological impression 1, kinetic description 1, overall lesion score 2, biopsy not performed, homogeneous enhancement, scalloped margin, lobulated in shape, proximity to: skin = 18 mm, chest wall = 21 mm, nipple RAC = 66 mm
- index lesion in contralateral breast at site 'left inner quadrant':
  - *initial scan* size = 6 mm, morphological impression 0, kinetic description 2, overall lesion score 2, biopsy negative, homogeneous enhancement, smooth margin, oval in shape, proximity to: skin = 10 mm, chest wall = 45 mm, nipple RAC = 21 mm
  - *repeat scan* size = 8 mm, morphological impression 0, kinetic description 2, overall lesion score 2, biopsy not performed, homogeneous enhancement, smooth margin, oval, proximity to: skin = 10 mm, chest wall = 45 mm, nipple RAC = 21 mm.

Although the overall lesion score for the last two patients was '2' on both the initial and repeat MR examinations, repeat XRM showed no malignant features or change in appearance over a 12 month period and as a consequence the decision at multi-disciplinary meeting was that neither was clinically significant.

As with the interpretation of the < 5-mm MRI-only-detected lesions, due to the problems associated with missing data, the results of the clinical significance of 5-mm biopsy-negative MRI-only-detected lesions are inconclusive.

Of the 66 patients with MRI-only-detected ≥ 5-mm biopsy-negative lesions, six patients had an unknown enhancing lesion remaining on repeat MRI, i.e. at least one ≥ 5-mm lesion that was biopsy negative or, if biopsy was not performed, the overall lesion score was < 2. For one patient, two lesions were evident on repeat MRI, both homogenously enhancing, one measuring 4 mm

and the other 6 mm in diameter, and neither considered to be clinically significant. However, we were unable to identify corresponding lesions on the original MR scan, in which enhancement within the lesion was heterogeneous. The median size of the lesions of the remaining five patients was 6.0 mm (range 5.0–35.0), and enhancement within lesion was homogenous for 4/5 patients (80.0%) and heterogeneous for 1/5 (20.0%).

Local recurrence-free interval

Local recurrence-free interval was calculated as the time from randomisation to the date of local recurrence, or death due to breast cancer. There were four patients who did not undergo surgery; therefore, these patients were censored at randomisation. There was one further patient who had a local recurrence; however, only the year and month were known, therefore this patient was assumed to have had a local recurrence on the 15th of the month. Patients with missing follow-up data, or who were alive and local recurrence-free at the time of analysis, were censored at the last date they were known to be alive and local recurrence free.

The median length of follow-up of all patients was 2.1 years (range 0.0–5.7), and this did not differ between the two arms. *Figure 3* displays Kaplan–Meier curves of local recurrence-free intervals. Local recurrence-free interval rate at 1 year post randomisation was 99.87% (95% CI 99.05% to 99.98%) for patients randomised to MRI, compared with 99.73% (95% CI 98.93% to 99.93%), for patients randomised to no MRI. At 3 years, local recurrence-free interval rate was 93.90% (95% CI 90.94% to 95.92%) for patients randomised to MRI, compared with 96.46% (95% CI 93.88% to 97.96%) for patients randomised to no MRI. It was noted that there were more deaths due to breast cancer in the MRI arm (16/30, 53.3%) than in the no MRI arm (4/15, 26.7%), which explains the differences in local recurrence-free interval between the arms (since the number of local recurrences is similar between the two). These excess deaths in the MRI arm had previously been acknowledged by the independent DMEC and were thought to be due to chance.

Cox's proportional hazards model was fitted to adjust for the minimisation factors. The hazard ratio for MRI versus no MRI was 2.02 (95% CI 1.09 to 3.75), indicating an increased risk of local-recurrence or death due to breast cancer in the MRI arm compared with the no-MRI arm, reflecting the previous results.

Adverse events

Adverse events relating to the intervention were not routinely collected.

Quality assurance findings

In total, 171 MR scans (21% of all scans) were requested for re-reading. Eighteen of these could not be recovered, primarily due to local archiving problems. Of the remaining 153 scans, 12 (7.8%) were non-compliant with the technical scanning protocol, and five (3.2%) were considered as misreported. Of the misreported MR scans, three were based on technically non-compliant scans, and two used technically compliant scans. Findings are summarised in *Table 22*.

Irretrievable scans, unreadable scans and technical failures were concentrated at six small centres, which accounted for 43 (5.2%) scans undertaken in the trial. The remaining 39 centres, accounting for 94.8% of scans conducted during the trial, reported no technical failures, and had a misreporting rate of 1.4%. The performance of the above mentioned six centres and of the remaining 39 centres is summarised in *Table 23*.

Problems were particularly concentrated at one centre, which accounted for 24 of the total scans undertaken for the trial. Because only a sample of patient scans were re-reported, no patient data was excluded from the trial on the basis of the findings of the QA, as this could introduce bias. However, the primary end point analysis was conducted both including and excluding the most problematic centre, which accounted for 24 scans in the trial. The results from the analysis excluding this centre were consistent with those of the main ITT analysis.

Clinical results summary

- There was no evidence of a difference in the reoperation rate between the MRI and no-MRI groups. In the primary ITT analysis, 18.8% of patients in the MRI group underwent a reoperation, compared with 19.3% in the no-MRI group, with an odds ratio of 0.96 (95% CI 0.75 to 1.24) and p-value of 0.7691.
- Overall, the best agreement between all imaging modalities and histopathology, with respect to tumour size and extent of disease, was found in patients who were aged over 50,

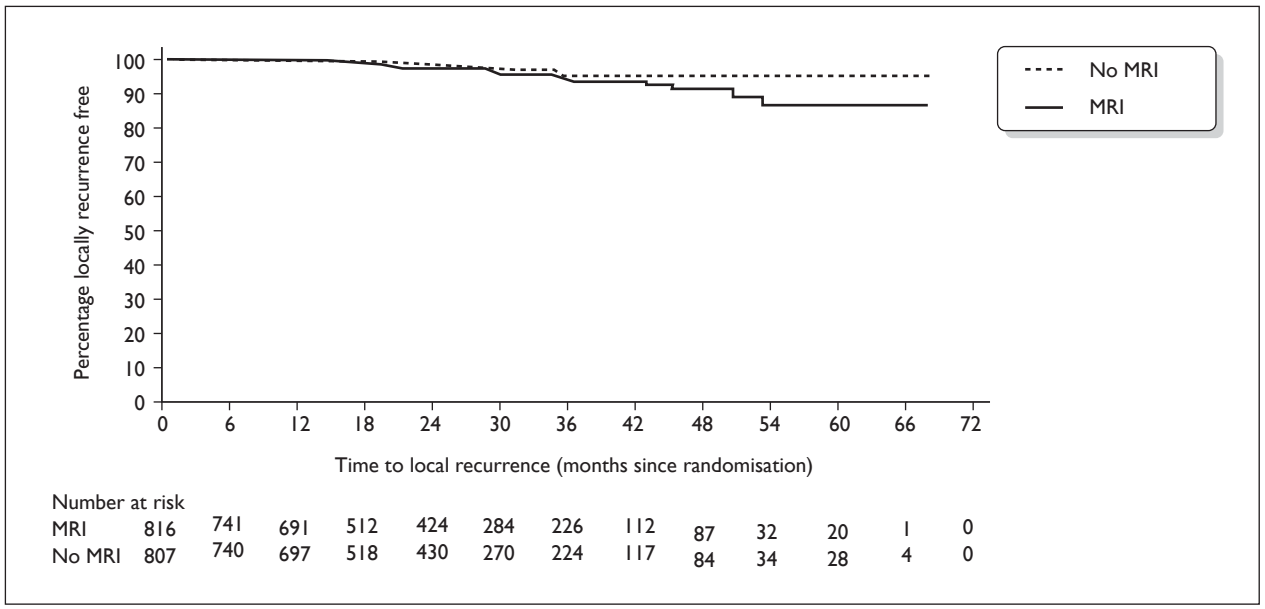

FIGURE 3 *Local recurrence-free interval: Kaplan–Meier curves.*

TABLE 22 *Summary quality assurance findings of re-read MR scans*

		Reporting standard			
		Unreadable	**Failure**	**Pass**	**Total**
Technical standard	**Failure**	6	3	2	12
	Pass	0	2	139	141
	Total	6	5	141	153

TABLE 23 *Summary quality assurance findings across groups of centres*

	MR scans				
Centres	**Requested[a]**	**Irretrievable/unreadable[b]**	**Technical failure[c]**	**Misreported[d]**	**Trial total[e]**
6 centres	31	15	12[f]	3[g]	43[h]
39 centres	140	3[i]	0	2[i]	771
All 45 centres	171	18	12	5	814

a Request made to centre for scan retrieval.
b Scans that could not be retrieved or were unreadable due to format /recording problems.
c Scan was not compliant with the trial's MR technical protocols.
d Two re-readings of the scan by radiologists concluded that the original reading was incorrect.
e Number of scans undertaken for the trial as a whole.
f Five centres.
g These three scans were not compliant with the MR technical protocols.
h One centre accounted for 24 scans.
i Three centres.
j Two centres.

had ductal tumours NST and who were node negative.

- The sensitivity and positive predictive values of MRI for determining patient management were 50.0% and 61.8%, respectively, and of the 58 patients in the MRI arm who underwent a mastectomy, 16 (27.6%) were classed as being pathologically avoidable.
- Exploratory analyses considering the level of agreement in size of tumour between histopathology and each imaging method identified all imaging methods to have borderline moderate to fair agreement with histopathology (weighted kappa statistics range 0.3803–0.4767). In general, the imaging methods tended to upstage smaller tumours and downstage larger tumours.
- Additional findings in the contralateral breast were identified for 62 patients (7.6%) via MRI, resulting in 12 patients (19.4%) undergoing WLE and one patient (1.6%) undergoing mastectomy.
- There were no significant differences in the proportion of patients receiving chemotherapy, radiotherapy or additional adjuvant therapies between the groups. Overall, within 6 months of initial surgery, 29.1% of patients received chemotherapy, 57.9% of patients received radiotherapy, and 51.3% of patients received additional adjuvant therapies.
- None of the 25 patients with MR-only-detected < 5-mm lesions had a clinically significant lesion evident at their 12-month repeat MR scan. Of the 66 patients with ≥ 5-mm biopsy-negative lesions, only three had potentially clinically significant lesions at their repeat MR scan; however, this was based on overall lesion score as these lesions were not biopsied.

Chapter 4
Quality of life results

The QoL population consists of 1446/1623 patients (89.1%) (MRI: 727, no MRI: 719). Baseline characteristics, mammography and USS findings, MRI findings, surgery characteristics and pathological findings of the QoL population were summarised and informally compared with those of the ITT population. Characteristics were very similar to those of the ITT population, and full summaries can be found in Appendix 16.

Assessment of compliance and missing data

Table 24 displays summaries of questionnaire timing for all patients in the QoL population. At 8 weeks post randomisation, the median time from randomisation to questionnaire completion was 8.4 weeks (range 1.6–25.4). At 6 months post surgery, the median time from surgery to questionnaire completion was 6.0 months (range 1.1–9.8). At 12 months post surgery, the median time from surgery to questionnaire completion was 12.0 months (range 8.2–20.9). Additionally, *Table 25* displays the percentage of expected questionnaires that are missing for each QoL time point (i.e. baseline, 8 weeks post randomisation, and 6 and 12 months post initial surgery). The number of expected questionnaires excludes deceased patients and, at 6 and 12 months post surgery, patients who did not undergo surgery, but includes patients who withdrew or were withdrawn from the QoL study for any reason post randomisation. Compliance is good with rates being similar between the two arms at all time points. At each time point there were between 11% and 15% of patients who did not complete a whole QoL form. Compliance decreases over time but even at 1 year post initial surgery, compliance is high at 86.9% and 84.2% in the MRI and no-MRI arms, respectively. Reasons for missing questionnaires are not available.

Missing data were assessed in detail and overall there were very few missing data for individual QoL questions and QoL subscales, at most 5% for any single subscale score. Additionally, mean QoL scores were grouped by the timing of patients' last assessments, and showed little difference in mean scores according to last assessment, indicating that missing data does not appear to be influenced by patients QoL. Summary tables and figures of missing data assessments are not given here. Data were deemed to be missing at random. In addition, the proportions of missing data at each time point were almost identical between the two arms. Since multilevel modelling was used, which accounts for missing data at the time point not of interest, and given the proportions of missing data were the same between the two arms, imputation was not deemed necessary for this analysis. Data summaries are presented for available case data.

Only prerandomisation assessments were included as baseline measurements (or assessments completed post randomisation, but before the patient was informed of their allocation result). Data were analysed using a time frame of ± 14 days around the expected date of completion of the questionnaire at 8 weeks post randomisation, a time frame of ± 28 days around the expected date of completion of the questionnaires at 6 months and ± 56 days around the expected date of the 1 year-post-surgery questionnaire. *Table 26* displays the number and percentage of questionnaires received that were completed in the relevant time windows. Compliance within the time windows is very good at baseline and 6 and 12 months post initial surgery; however, it is lower at 8 weeks post randomisation, with only 66.7% and 66.3% of patients completing within 6–10 weeks post randomisation in the MRI and no-MRI arms, respectively. Using a time frame of ± 21 days rather than ± 14 days, questionnaires were completed in the window for 1035 patients (81.0%) [MRI: 522 (80.8%); no MRI: 513 (81.2%)]. In order to establish whether to conduct sensitivity analyses using the ± 21 days time window, data were summarised using median and mean QoL scores, with corresponding 95% CIs for the means for each time window. Results were almost identical for the two time windows, therefore sensitivity analyses were not deemed necessary and the original time window of ± 14 days was used.

TABLE 24 *QoL: questionnaire timing for all patients*

	MR scan (*n* = 727)	No MR scan (*n* = 719)	Total (*n* = 1446)
Baseline questionnaire timing (n %)			
Prerandomisation	647 (89.0)	635 (88.3)	1282 (88.7)
Postrandomisation	55 (7.6)	53 (7.4)	108 (7.5)
N/A (no baseline assessment)	15 (2.1)	21 (2.9)	36 (2.5)
Missing data	10 (1.4)	10 (1.4)	20 (1.4)
Prerandomisation baseline: time since randomisation (days)[a]			
Mean (SD)	–0.6 (1.47)	–0.7 (2.05)	–0.6 (1.78)
Median (range)	0.0 (–18.0 to 0.0)	0.0 (–22.0 to 3.0)	0.0 (–22.0 to 3.0)
Missing	0	0	0
8 weeks post randomisation: time since randomisation (days)			
Mean (SD)	62.9 (20.73)	61.4 (19.74)	62.2 (20.25)
Median (range)	59.0 (18.0 to 161.0)	58.0 (11.0 to178.0)	59.0 (11.0 to 178.0)
Missing	80	87	167
6 months post initial surgery: time since initial surgery (days)			
Mean (SD)	186.2 (21.76)	187.1 (22.54)	186.6 (22.15)
Median (range)	184.0 (35.0 to 286.0)	184.0 (59.0 to 297.0)	184.0 (35.0 to 297.0)
Missing	95	95	190
1 year post initial surgery: time since initial surgery (days)			
Mean (SD)	368.9 (23.47)	368.9 (21.49)	368.9 (22.52)
Median (range)	366.0 (250.0 to 635.0)	366.0 (318.0 to 570.0)	366.0 (250.0 to 635.0)
Missing	95	113	208

[a] This includes patients who completed their questionnaire *after* randomisation but *before* they were told their randomisation allocation result.

Data summaries

Table 27 displays QoL summaries for those patients who completed questionnaires within the relevant time frames.

Overall, QoL scores were similar between the two treatment groups, with QoL decreasing minimally between baseline and 8 weeks post randomisation, then recovering at between 6 and 12 months post initial surgery.

At each time point, physical, social/family and functional well-being scores were above the normative data described by Webster and colleagues[75] for a general US population. Physical and functional well-being decreased between baseline and 8 weeks post randomisation, then recovered between 8 weeks post randomisation and 12 months post initial surgery, whereas social/family well-being and breast cancer concerns scores did not change. Emotional well-being improved between baseline and 8 weeks post randomisation, then did not change.

HADS anxiety and depression scores were also similar between the treatment groups, with median anxiety scores of 7 at baseline, which then decreased between baseline and 8 weeks post randomisation and then stabilised. Depression scores were low at baseline and did not change thereafter.

DOI: 10.3310/hta14010

TABLE 25 *QoL: percentage of expected questionnaires that are missing*

	Baseline				8 weeks post randomisation				6 months post initial surgery				1 year post initial surgery					
	MR scan		No MR scan		MR scan		No MR scan		MR scan		No MR scan		MR scan		No MR scan		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Missing																		
Yes	15	2.1	21	2.9	81	11.1	87	12.1	95	13.1	95	13.3	95	13.1	113	15.8	730	12.6
No	712	97.9	698	97.1	646	88.9	632	87.9	629	86.9	621	86.7	629	86.9	602	84.2	5041	87.4
Total	**727**	**100.0**	**719**	**100.0**	**727**	**100.0**	**719**	**100.0**	**724**	**100.0**	**716**	**100.0**	**724**	**100.0**	**715**	**100.0**	**5771**	**100.0**

TABLE 26 *QoL: percentage of questionnaires completed in relevant time windows*

	Baseline				8 weeks post randomisation				6 months post initial surgery				1 year post initial surgery					
	MR scan		No MR scan		MR scan		No MR scan		MR scan		No MR scan		MR scan		No MR scan		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
In window?																		
Yes	647	90.9	635	91.0	431	66.7	419	66.3	563	89.5	547	88.1	614	97.6	589	97.8	4445	86.0
No	65	9.1	63	9.0	215	33.3	213	33.7	66	10.5	74	11.9	15	2.4	13	2.2	724	14.0
Total	**712**	**100.0**	**698**	**100.0**	**646**	**100.0**	**632**	**100.0**	**629**	**100.0**	**621**	**100.0**	**629**	**100.0**	**602**	**100.0**	**5169**	**100.0**

TABLE 27 *QoL: HADS and FACT-B summaries for all patients who completed questionnaires within the relevant time windows*

	MR scan					No MR scan				
	n	**Median**	**Mean**	**LCL**	**UCL**	***n***	**Median**	**Mean**	**LCL**	**UCL**
Baseline										
HADS score	644	8.0	9.5	9.0	10.0	634	9.0	10.0	9.5	10.5
HADS anxiety score	644	7.0	7.1	6.7	7.4	634	7.0	7.4	7.1	7.7
HADS depression score	645	1.0	2.4	2.2	2.6	634	2.0	2.6	2.4	2.8
FACT-B total	613	114.0	110.4	109.0	111.8	613	114.0	110.3	109.0	111.7
FACT-G total	624	88.0	84.6	83.5	85.6	619	88.0	84.7	83.6	85.7
FACT-B physical well-being	640	25.7	24.6	24.3	24.8	632	25.8	24.7	24.4	24.9
FACT-B social/family well-being	637	26.0	24.8	24.4	25.1	631	26.0	24.5	24.2	24.9
FACT-B emotional well-being	635	14.0	12.9	12.5	13.2	626	14.0	13.1	12.7	13.4
FACT-B functional well-being	640	24.0	22.3	21.9	22.7	629	24.0	22.4	22.0	22.8
FACT-B additional concerns	634	26.0	25.8	25.3	26.2	626	26.0	25.7	25.2	26.1
Trial Outcome Index	624	75.0	72.7	71.7	73.7	619	74.0	72.7	71.8	73.6
6 months post initial surgery										
HADS score	558	7.0	8.3	7.8	8.8	545	7.0	8.8	8.2	9.3
HADS anxiety score	558	4.0	5.0	4.7	5.3	545	5.0	5.3	4.9	5.6
HADS depression score	558	2.0	3.3	3.0	3.6	546	2.0	3.5	3.2	3.8
FACT-B total	545	112.0	107.2	105.3	109.1	533	111.0	107.2	105.4	109.1
FACT-G total	549	87.0	82.5	81.1	83.9	535	86.0	82.4	81.0	83.8
FACT-B physical well-being	559	24.0	22.3	21.9	22.7	541	24.0	22.1	21.7	22.6
FACT-B social/family well-being	559	25.0	23.7	23.3	24.1	540	25.7	23.7	23.3	24.2
FACT-B emotional well-being	553	16.0	15.5	15.2	15.9	541	16.3	15.4	15.1	15.8
FACT-B functional well-being	554	23.0	21.0	20.5	21.5	542	22.0	21.1	20.6	21.6
FACT-B additional concerns	556	26.0	24.7	24.1	25.3	543	26.0	24.8	24.2	25.3
Trial Outcome Index	547	72.0	67.9	66.5	69.3	535	71.0	68.1	66.7	69.4

TABLE 27 *QoL: HADS and FACT-B summaries for all patients who completed questionnaires within the relevant time windows (continued)*

	MR scan					No MR scan				
	n	**Median**	**Mean**	**LCL**	**UCL**	***n***	**Median**	**Mean**	**LCL**	**UCL**
8 weeks post randomisation										
HADS score	430	7.0	8.7	8.1	9.3	417	7.0	8.9	8.2	9.5
HADS anxiety score	430	5.0	5.6	5.2	5.9	417	5.0	5.6	5.3	6.0
HADS depression score	430	2.0	3.2	2.9	3.5	418	2.0	3.2	2.9	3.5
FACT-B total	421	112.0	107.2	105.3	109.2	412	111.0	107.4	105.4	109.3
FACT-G total	420	86.0	82.3	80.8	83.8	412	85.3	82.2	80.7	83.7
FACT-B physical well-being	423	24.0	22.1	21.6	22.6	417	24.0	22.4	21.9	22.8
FACT-B social/family well-being	426	26.0	24.6	24.2	25.1	416	26.0	24.2	23.7	24.7
FACT-B emotional well-being	425	16.0	15.1	14.7	15.5	416	16.0	15.1	14.6	15.5
FACT-B functional well-being	428	22.0	20.5	19.9	21.1	416	22.0	20.5	20.0	21.1
FACT-B additional concerns	429	26.0	24.9	24.3	25.5	418	26.0	25.2	24.6	25.8
Trial Outcome Index	422	70.0	67.5	66.1	69.0	415	71.0	68.1	66.7	69.5
1 year post initial surgery										
HADS score	607	7.0	8.1	7.6	8.6	586	7.0	8.2	7.6	8.7
HADS anxiety score	609	5.0	5.2	4.9	5.5	586	5.0	5.3	4.9	5.6
HADS depression score	608	1.6	2.9	2.6	3.1	586	2.0	2.9	2.7	3.2
FACT-B total	583	115.8	109.9	108.2	111.6	569	115.0	110.6	109.0	112.3
FACT-G total	586	88.9	84.3	83.0	85.5	575	89.0	84.7	83.5	86.0
FACT-B physical well-being	601	25.0	23.5	23.1	23.8	583	25.0	23.6	23.3	24.0
FACT-B social/family well-being	605	25.7	23.6	23.2	24.0	582	25.7	23.5	23.0	23.9
FACT-B emotional well-being	595	16.0	15.3	15.0	15.6	583	16.0	15.5	15.2	15.8
FACT-B functional well-being	604	23.6	21.9	21.4	22.3	587	24.0	22.1	21.6	22.5
FACT-B additional concerns	609	27.0	25.7	25.1	26.2	583	27.0	25.8	25.3	26.3
Trial Outcome Index	590	75.3	71.1	69.9	72.3	576	75.0	71.6	70.4	72.7

LCL, lower confidence limit; UCL, upper confidence limit.

TABLE 28 *QoL: HADS summary (categorical) for all patients*

	Baseline			8 weeks post randomisation		
	MR scan, *n* (%)	**No MR scan, *n* (%)**	**Difference (%), 95% CI**	**MR scan, *n* (%)**	**No MR scan, *n* (%)**	**Difference (%), 95% CI**
HADS anxiety score (categorical)						
Normal	375 (58.0)	334 (52.6)	–5.4 (–10.95 to 0.23)	302 (70.1)	303 (72.3)	2.2 (–4.08 to 8.57)
Borderline	146 (22.6)	163 (25.7)	3.1 (–1.73 to 7.94)	80 (18.6)	61 (14.6)	–4.0 (–9.23 to 1.22)
Probably clinically significant	123 (19.0)	137 (21.6)	2.6 (–1.99 to 7.12)	48 (11.1)	53 (12.6)	1.5 (–3.08 to 6.10)
Missing	3 (0.5)	1 (0.2)		1 (0.2)	2 (0.5)	
HADS depression score (categorical)						
Normal	604 (93.4)	589 (92.8)	–0.6 (–3.54 to 2.34)	386 (89.6)	373 (89.0)	–0.5 (–4.93 to 3.86)
Borderline	24 (3.7)	34 (5.4)	1.6 (–0.79 to 4.08)	31 (7.2)	27 (6.4)	–0.7 (–4.37 to 2.87)
Probable clinically significant	17 (2.6)	11 (1.7)	–0.9 (–2.65 to 0.86)	13 (3.0)	18 (4.3)	1.3 (–1.48 to 4.04)
Missing	2 (0.3)	1 (0.2)		1 (0.2)	1 (0.2)	
	6 months post initial surgery			**1 year post initial surgery**		
	MR scan, *n* (%)	**No MR scan, *n* (%)**	**Difference**	**MR scan, *n* (%)**	**No MR scan, *n* (%)**	**Difference**
HADS anxiety score (categorical)						
Normal	412 (73.2)	394 (72.0)	–1.2 (–6.58 to 4.28)	451 (73.5)	431 (73.2)	–0.3 (–5.44 to 4.89)
Borderline	102 (18.1)	90 (16.5)	–1.7 (–6.29 to 2.96)	101 (16.4)	88 (14.9)	–1.5 (–5.78 to 2.77)
Probably clinically significant	44 (7.8)	61 (11.2)	3.3 (–0.29 to 6.96)	57 (9.3)	67 (11.4)	2.1 (–1.52 to 5.70)
Missing	5 (0.9)	2 (0.4)		5 (0.8)	3 (0.5)	
HADS depression score (categorical)						
Normal	484 (86.0)	473 (86.5)	0.5 (–3.73 to 4.74)	542 (88.3)	534 (90.7)	2.4 (–1.24 to 6.02)
Borderline	55 (9.8)	51 (9.3)	–0.4 (–4.08 to 3.19)	49 (8.0)	37 (6.3)	–1.7 (–4.77 to 1.37)
Probably clinically significant	19 (3.4)	22 (4.0)	0.6 (–1.75 to 3.05)	17 (2.8)	15 (2.5)	–0.2 (–2.21 to 1.76)
Missing	5 (0.9)	1 (0.2)		6 (1.0)	3 (0.5)	

In addition to the summary scores presented in *Table 27*, the HADS questionnaire was also summarised categorically, with anxiety or depression scores of 7, indicating that a patient shows normal levels of anxiety or depression, a score of 8–10 indicating that the patient shows borderline levels of anxiety or depression, and a score of greater than 10 indicating that the patient shows levels of anxiety or depression that are probably clinically significant.[46] *Table 28* displays these results. Considering anxiety, at baseline the two treatment groups were similar and the percentage of patients who had clear signs of anxiety was moderate [MRI: 123/647 (19.0%); no MRI: 137/635 (21.6%)]. At 8 weeks post randomisation, although the groups were also similar, the percentage of patients who had clear signs of anxiety decreased [MRI: 48/431 (11.1%); no MRI: 53/419 (12.6%)]. At 6 months post initial surgery, 44/563 (7.8%) patients randomised to MRI had probably clinically significant signs of anxiety, compared with 61/547 (11.2%) patients randomised to no MRI; at 12 months post surgery 57/614 (9.3%) patients randomised to MRI had probably clinically significant signs of anxiety, compared with 67/589 (11.4%) patients randomised to no MRI.

The percentage of patients who had probably clinically significant signs of depression was less than 5%, at all assessment times. At baseline, 17/647 patients (2.6%) randomised to receive an MRI and 11/635 patients (1.7%) randomised to no MRI had probably clinically significant signs of depression. These percentages increased slightly at 8 weeks post randomisation and 6 months post initial surgery, and decreased again at 12 months post initial surgery.

Since the number of patients completing QoL questionnaires at each time point varies, the summary statistics cannot be validly compared over time, as a different subset of patients was observed at each point. QoL scores for subsets of patients with differing lengths of complete follow-up were calculated and showed similar profiles to those presented above; therefore, additional summaries are not presented.

Treatment comparisons at each time point

Mean adjusted for baseline QoL scores and 95% CIs, and corresponding differences between the trial arms at each time point, were calculated; however, results were very similar to the non-adjusted results presented above and are therefore not displayed.

Subsequent to developing the protocol for the COMICE trial, Eton *et al.*[76] established the minimally important difference (MID) in QoL measured using the FACT-B. This corresponds to the minimum difference in QoL that is both clinically *and* statistically significant, as it was established using both distribution- and anchor-based methods. In their paper, the authors outline a difference of 5–6 points to be the MID for the TOI. As can be seen by considering the TOI scores in *Table 27*, differences between the trial arms at each time point are minimal and do not reach the MID. Overall, QoL was found to be very similar between the two arms, with only minor changes in QoL over time.

Quality of life results summary

- The QoL substudy population was representative of the population on which clinical inferences were made.
- Overall, QoL scores were similar between the two treatment groups, with QoL decreasing minimally between baseline and 8 weeks post randomisation, then recovering at between 6 and 12 months post initial surgery.
- Differences between the two trial arms at each time point for the TOI score were minimal and did not reach the minimal important difference of 5–6 points.
- HADS anxiety and depression scores were also similar between the treatment groups, with median anxiety scores of seven at baseline, which then decreased slightly between baseline and 8 weeks post randomisation and then stabilised.
- Depression scores were low at baseline and did not change thereafter.

Chapter 5
Economic evaluation results

Resource use

The economic analysis was carried out once all patients had been followed up for at least 12 months. Details of some of the key resource use from the initial surgery can be found in Appendix 17 (Summary of key resource use from initial surgery). It should be noted that we have attempted not to replicate information on resource use that is contained in the clinical analysis in earlier chapters. The times in the anaesthetic room, theatre, recovery room and for axillary surgery were broadly similar across the two arms, although these were all marginally higher in the MRI arm. This was as expected, as more patients in this arm received surgery other than WLE surgery. Whilst marginally more patients in the no-MRI arm experienced complications, the number of patients who were returned to theatre was very similar in both arms. Similarly, the number requiring fluid replacement was very similar in the two arms. Only one patient was placed in a high-dependency ward following surgery.

Summaries of the resource use in the 12-month period following initial surgery are also given in Appendix 17 (*Table 58*). Resource use in the trial is broadly similar across the two arms. Slightly more patients in the MRI arm experienced complications between leaving hospital and their first post-operative follow-up. However, even though the number of patients who experienced complications was larger, the numbers who were admitted to hospital due to these complications was lower than in the no MRI arm of the trial. More patients in the no MRI arm required a repeat operation than those in the MRI arm. In contrast to the first post operative follow-up, more patients in the no MRI arm experienced complications after leaving hospital, whilst more in the MRI arm were hospitalised as a result. However, as with the first postoperative follow-up, the numbers are similar. At the 6-month follow-up, slightly more patients in the no-MRI arm had undergone an oophorectomy, but more patients in the MRI arm had undergone further surgery. At the 12-month follow-up, more patients in the MRI arm had been readmitted to hospital, or undergone an oophorectomy or other surgery. More patients in the MRI arm had received chemotherapy but less had received radiotherapy; however, the differences between the two arms are only marginal.

Unit costs

Unit costs at 2006–7 prices were used to value the resource use measured in the trial. These were taken to be long-term average costs. Details of some of the unit costs for key resource use in the trial can also be found in Appendix 17 (Prices and unit costs of major resource items). As explained in the methods chapter of this report, it is the incremental cost is of interest in this trial. As such when resource use was considered to be broadly equivalent across the two arms, the resources were not costed (for example, conventional triple assessment was not costed).

Missing data

Table 29 below describes the extent of missingness of the data once the resource use data was costed and aggregated into various cost categories. As can be seen from the table, certain components were subject to a large amount of missing data, in particular the cost of initial surgery, which is an important cost contributor but which had 44.79% of observations missing. *Table 29* also describes the extent of missingness of the EQ-5D scores at baseline, 8 weeks post randomisation, and at 6 and 12 months post initial surgery. The dearth of cost of initial surgery data is due to a combination of missing forms, for which no data on costs were available, and also due to poor recording of times in the various aspects of surgery. Poor recording of times resulted in all the other costs accounted for in initial surgery being ignored as aggregation into the component was only possible when data on all of the resource usage of initial surgery was available. This data was primarily completed by the theatre staff or surgeons, and as such resulted in relatively poor completion in comparison with other data, which was routinely collected by research staff. The missing data in the other cost components and the EQ-5D data was largely a result of missing forms.

TABLE 29 *Summary of missing data*

Cost category	Missing observations	Percentage of total
Cost of initial surgery	727	44.79
Cost of postoperative complications (still in hospital from initial surgery)	3	0.18
Cost of initial hospital stay	16	0.99
Cost of MRI (first and any repeat)	4	0.25
Cost of repeat operation	13	0.80
Cost of follow-up in first 6 months after surgery	55	3.39
Cost of follow-up in first 12 months after surgery	167	10.29
Chemotherapy cost	154	9.49
Radiotherapy cost	216	13.31
GP costs at 8 weeks post randomisation	271	16.70
GP costs at 6 months post initial surgery	346	21.32
GP costs at 12 months post initial surgery	526	32.41
Baseline EQ-5D score	225	13.86
EQ-5D score 8 weeks post randomisation	285	17.56
EQ-5D score 6 months post initial surgery	349	21.50
EQ-5D score 12 months post initial surgery	535	32.96

Imputed cost data

As a result of the missing data problems described above, various cost components were imputed using multiple ICE (this is described in the methods section of this report). *Table 30* details the mean costs, standard errors and 95% CIs for the various aggregated cost categories. The CIs have been calculated assuming that the cost components follow a gamma distribution.

As can be seen from the table, the mean cost of initial surgery was higher in the MRI arm, as expected given the longer duration of the surgery and more non-WLE surgeries being conducted. The cost of staying in hospital following the initial surgery was also higher in the MRI group, reflecting the slightly longer mean length of stay than the non-MRI arm (3.55 nights compared with 2.86 nights). The MRI cost was larger in the MRI arm, as was expected. Due to the larger number of patients in the non-MRI arm who received a repeat operation, the costs were higher. However, the CIs of the mean estimates for both arms do overlap. The mean cost of follow-up at 6 months is very similar in both arms (£102.06 in the MRI arm compared with £105.02 in the non-MRI arm). The mean cost of follow-up at 12 months is higher in the MRI arm although, again, the CIs overlap. The mean cost of chemotherapy is higher in the MRI arm, but this partially offset by a lower mean cost of radiotherapy. GP costs are broadly similar between the arms at 8 weeks post randomisation, and 6 and 12 months post initial surgery.

The mean total cost of the resources measured in this cost analysis was higher in the MRI arm than in the non-MRI (£5508.40 compared with £5213.50, resulting in an incremental cost of £294.90). This is largely a result of the extra cost of MRI (an additional £236.45 for the MRI arm compared to the non-MRI arm) as the other cost categories are reasonably balanced between arms. Given the lack of difference in clinical end points in the trial, the similar total costs are as expected with the difference appearing to be driven by the one clear resource use difference between the two arms – the use of MRI.

Regression analyses on imputed cost data

Table 31 presents the regression of total cost on treatment arm, age, BMI and whether the patient has had a recurrence at 12 months post

TABLE 30 *Imputed cost table*

Cost category	Mean (£)	Standard error	Lower 95% CI	Upper 95% CI
Cost of initial surgery				
MRI arm	465.38	10.19	444.79	485.98
No MRI	438.39	11.3954	414.15	462.63
Cost of postoperative complications (still in hospital from initial surgery)				
MRI arm	7.03	2.46165	3.54	13.98
No MRI	4.63	1.62614	2.32	9.22
Cost of initial hospital stay				
MRI arm	714.60	34.9942	645.93	783.27
No MRI	663.16	32.6363	599.11	727.20
Cost of MRI (first and any repeat)				
MRI arm	239.94	50.4457	140.95	338.93
No MRI	3.49	0.737721	2.04	4.94
Cost of repeat operation				
MRI arm	327.43	25.0281	278.31	376.55
No MRI	382.09	29.1883	324.81	439.37
Cost of follow-up in first 6 months after surgery				
MRI arm	102.06	19.5549	70.05	148.69
No MRI	105.02	19.9424	72.35	152.45
Cost of follow-up in first 12 months after surgery				
MRI arm	385.11	44.4571	306.91	483.25
No MRI	370.56	45.6576	290.23	473.12
Chemotherapy cost				
MRI arm	1473.83	86.6983	1303.70	1643.97
No MRI	1428.85	83.9945	1264.02	1593.67
Radiotherapy cost				
MRI arm	1785.40	37.7097	1711.31	1859.49
No MRI	1789.38	39.4394	1711.58	1867.18
GP costs at 8 weeks post randomisation				
MRI arm	58.64	1.91292	54.89	62.39
No MRI	59.33	1.98996	55.42	63.24
GP costs at 6 months post initial surgery				
MRI arm	52.25	2.41301	47.42	57.09
No MRI	51.89	2.29544	47.33	56.45
GP costs at 12 months post initial surgery				
MRI arm	44.99	3.06173	38.51	51.48
No MRI	43.46	2.92713	37.29	49.63
Total cost of resources included in the cost analysis				
MRI arm	5508.40	120.85	5271.17	5745.62
No MRI	5213.50	117.243	4983.09	5443.91

initial surgery. This has been performed using a generalised linear model with an identity link function and assuming a gamma distribution. The regression allows us to look at the effects of age, BMI, recurrence status and treatment arm have on total costs. An example of how these results can be interpreted is presented below.

For example, a 60-year-old in the MRI arm who had not suffered a recurrence and with a BMI of 30 would have the following cost: total cost = (292.35×1) + (–109.71×60) + (2882.67×0) + (55.29×30) + 10050 = £5418.64.

Table 31 suggests the mean additional cost per patient of the MRI arm is £292.35 after controlling for the other variables included as regressors in the model. However, this is not statistically significant at a 5% level. The negative coefficient on age suggests that total costs decrease with a patient's age. The positive coefficient on BMI suggests that a patient's total cost increases with their BMI. The results also suggest that patients who have had a recurrence have significantly higher costs than those who do not (£2882.67 more).

Imputed EQ-5D scores

As with the cost components, the large extent of missing data (see *Table 29*) in the EQ-5D scores made it necessary to impute the missing observations using multiple ICE. The EQ-5D mean scores, standard errors and 95% CIs are detailed in *Table 32*, by trial arm, for baseline, 8 weeks post randomisation, and 6 and 12 months post initial surgery.

The mean score in both arms fell from baseline to 8 weeks post randomisation and then increased at 6 months post initial surgery and again at 12 months post initial surgery. The scores are very similar between the arms at each time point, suggesting that there is no difference in HRQoL. Given the lack of difference in clinical end points between the two arms, the similar EQ-5D scores are as expected.

Regression analyses on imputed EQ-5D scores

Table 33 details the results of an ordinary least squares regression of the EQ-5D score at 12 months post initial surgery in the MRI arm, baseline EQ-5D, age, whether the patient had had a recurrence by 12 months and BMI. The coefficient on the baseline EQ-5D score is positive and statistically significant, which is expected given that other studies have shown that current HRQoL is related to previous HRQoL. The positive coefficient on age suggests that HRQoL increases with age, which is counterintuitive; however, the coefficient is not statistically significant at a 5% significance level. The negative coefficient on recurrence suggests that, on average, those patients who have had a recurrence will have a lower HRQoL than those who have not, which would be expected. However, again the coefficient is not statistically significant at a 5% significance level. This may be due to the small proportion of individuals who experienced a recurrence and, as such, the trial was not powered to identify this effect. The results also suggest that patients with a higher BMI, i.e. those who are more obese, will have a lower HRQoL, which would be expected.

The negative coefficient on the MRI arm suggests that after controlling for baseline EQ-5D, age, whether the patient had had a recurrence and BMI the mean score is lower for patients in the MRI arm, although the size of the coefficient suggests there is no difference between the arms. However, the coefficient is very small and is not statistically significant at a 5% level of significance and, as such, it would appear that there are no differences between the treatment arms. This result

TABLE 31 *Regression of total cost on treatment arm, age, BMI and recurrence status at 1 year*

	Coefficient	Standard error	*p*-value
MRI arm	292.35	163.65	0.075
Age	–109.71	7.52	<0.0001
Recurrence	2882.67	1460.57	0.049
BMI	55.29	15.36	<0.0001
Constant	10050	593.36	<0.0001

TABLE 32 *Summary of EQ-5D scores*

	Mean	Standard error	Lower 95%CI	Upper 95% CI
Baseline EQ-5D score				
MRI arm	0.8567	0.006535	0.843472	0.869939
No MRI	0.8601	0.006317	0.847457	0.872768
EQ-5D score 8 weeks post randomisation				
MRI arm	0.7791	0.00782	0.76342	0.79481
No MRI	0.7728	0.007923	0.756859	0.788701
EQ-5D score 6 months post initial surgery				
MRI arm	0.8040	0.009379	0.784391	0.823691
No MRI	0.7935	0.007767	0.778109	0.808941
EQ-5D score 12 months post initial surgery				
MRI arm	0.8101	0.0069	0.796531	0.823628
No MRI	0.8112	0.007194	0.796995	0.825319

TABLE 33 *Regression analysis of EQ-5D at 12 months post initial surgery on baseline EQ-5D, age, BMI and recurrence status at 1 year*

	Coefficient	Standard error	*p*-value
MRI arm	–0.00088	0.009312	0.924
Baseline EQ-5D score	0.522757	0.032484	< 0.001
Age	0.000214	0.000517	0.68
Recurrence	–0.0904	0.058853	0.13
BMI	–0.00199	0.00101	0.059
Constant	0.406104	0.05299	0

is consistent with the clinical analyses, in which no differences in primary end points were found between the arms.

Economic evaluation results summary

- The economic evaluation found that 12 months after initial surgery there was no statistically significant difference in HRQoL, as measured by the EQ-5D, between the two trial arms once baseline HRQoL and other covariates were controlled for. The nominal values of the point estimates of the mean changes between baseline and 12 months were also very similar.
- These results are consistent with the clinical and QoL findings that there is no difference between the trial arms in terms of outcomes.
- The economic evaluation did suggest that there may be a cost difference between the two trial arms, with the MRI arm having a larger mean resource cost per patient (£5508.40 compared with £5213.50), although the difference was not statistically significant once other covariates had been controlled for.

Chapter 6
NSSI study results

Clinical and sociodemographic characteristics

Forty-six (46%) of the 100 participants taking part in the NSSI study were randomised to receive MRI. Three patients who were randomised failed to have the scan. In one case, the scanner was undergoing repair, in the second case, the patient declined the scan and in the final case the patient was unable to fit into the scanner.

The median age of respondents was 59 years (range 37–82). Ninety-four women had breast conservative surgery (WLE or quadrantectomy) and six had unilateral mastectomy. The median number of nights in hospital postoperatively was two (range 1–10) and 15 (15%) of the women reported postsurgical complications.

Eighty-nine women expressed satisfaction with the shape of their breasts following surgery. Forty-three said they were very satisfied and 46 said they were satisfied. Ten women expressed dissatisfaction with their shape, two of whom were very dissatisfied.

In terms of adjuvant treatment, the women were having, or had had, the following treatments: chemotherapy – 38%; radiotherapy – 92%, hormone therapy – 78% and trastuzumab – 5%. The self-reported median waiting time post surgery for chemotherapy was 4 weeks (range 2–20 weeks) and for radiotherapy 12 weeks (range 2–36 weeks). Ten per cent of those receiving radiotherapy thought it had been given too late.

Response to randomisation

Fifty-five percent of the patients were pleased with the outcome of the randomisation process, although the majority of this group was randomised to have MRI. All of the patients randomised to have MRI were pleased with the outcome, whereas only 66% of patients in the 'no scan' group were pleased with the outcome (chi-squared test for trend = 53.35, $p < 0.0001$) (*Table 34*).

The majority of patients who had MRI were reassured by it. Two patients said it made them anxious and 16 were indifferent to the decision. Not having the scan made 18 of the patients anxious, and 32 said they were indifferent (chi-squared test for trend 33.397, $p < 0.0001$) (*Table 35*).

Procedural distress

Of those patients who received an MR scan, 34% indicated that they had found this 'distressing', and 14% found it 'very distressing'. In contrast, 1% of those having USS found this distressing (and she found it very distressing), 56% found biopsy distressing (14% very distressing), and 30% found mammography distressing (4% very distressing). The type of distress reported by the women is shown in *Table 36* (some women identified more than one type of distress).

Perceived choice of surgery

Thirty (30%) of the women said that they had been given a choice of operation and 26 (86%) found this helpful. Sixty-nine women said they had not been given a choice and of these 64 (92%) said that that had been helpful. One could not remember whether she had been given a choice. There was no significant difference between those given a choice and those not in terms of how helpful this was perceived to be (Fisher's exact $p = 0.448$).

Of the 98 women expressing an opinion 28 (93%) of the women who were given a choice of surgery felt that they had made the right decision about their operation. Sixty-three (92%) of the women who were not given a choice felt that the operation they had was the right one for them (*Table 37*). The proportion of women considering that they had received the right operation for them was unrelated to having been given a choice (Fisher's $p = 1.000$).

TABLE 34 *Response to randomisation: pleased/displeased*

	Pleased (*n*, %)	Indifferent/not sure (*n*, %)	Not pleased (*n*, %)
MRI	45 (45)	1 (1)	0 (0)
No MRI	10 (10)	25 (25)	19 (19)

TABLE 35 *Response to randomisation: reassured/anxious*

	Reassured (*n*, %)	Neither (*n*, %)	Anxious (*n*, %)
MRI	28 (28)	16 (16)	2 (2)
No MRI	4 (4)	32 (32)	18 (18)

TABLE 36 *Type of distress*

MR scan	
Claustrophobic	8
Noise	4
Panic	1
Other	3
Mammogram	
Discomfort	8
Painful	12
Panic	1
Other	4
USS	
Took a long time	1
Mental distress	1
Panic	1
Biopsy	
Very painful	20
Slightly painful	15
Uncomfortable	7
Noise	6
Mentally distressing	5
Bruising	3
Miscellaneous	3

TABLE 37 *Perceived choice of surgery*

	Right operation	
	Yes (*n*, %)	No (*n*, %)
Given a choice	28 (98)	2 (7)
Not given a choice	63 (93)	5 (7)

NSSI summary of results

- One hundred women from a range of recruiting centres participated in a non-schedule standardised interview study to evaluate aspects of their experience of treatment and study participation.
- All of the patients randomised to have MRI were pleased with the outcome of randomisation compared with 66% of patients in the no-MRI group.
- The majority of patients who had MRI were reassured by having it.
- Thirty-four per cent of patients randomised to MRI indicated that they had found this 'distressing', and 14% found it 'very distressing', whereas 1% found USS distressing, 56% found biopsy distressing and 30% found mammography distressing.

Chapter 7
Discussion

The NHS BSP is committed to reducing the reoperation rate for screen detected primary breast cancers to below 10%, whilst achieving a good cosmetic result by minimising the volume of tissue removed. In 2001–2 the reoperation rate for positive margins following WLE averaged at 14.2%, whilst in the most recent audit reported in 2006–7 this value had risen to 17.0%. This reoperation rate constitutes a considerable additional burden, both to the patient and the NHS. This trial sought to determine if the addition of MRI of the breast to current patient evaluation by triple assessment, using X-ray mammography and USS for lesion detection and characterisation, would reduce the reoperation rate in women with primary tumours who are scheduled for WLE.

Trial outcomes

Reoperation rate

The COMICE study is the first large pragmatic trial evaluating the effectiveness of MRI of small breast lesions, suitable for WLE. The study closed to recruitment on 31 January 2007, at which point 1625 patients had been randomised. Although this is lower than the target sample size calculation of 1840 patients, this still provided us with over 80% power to detect a 5% difference in reoperation rates. Of necessity, COMICE was a multicentre study utilising the services of 45 breast-care units throughout the UK and involving a total of 107 breast surgeons. This study demonstrates the ability of the UK to deliver a multicentre, large-scale trial acquiring standardised MR scans using the most commonly available MRI systems.

The results of the COMICE trial have shown that there is no significant benefit to patients scheduled to receive WLE, by adding MRI to conventional triple assessment. The overall reoperation rate for the COMICE trial was slightly higher than the NHS BSP 2006–7 rates at 19.0%, although this is within the 13–21% range quoted in 2006–7 for the UK. In the study as a whole, 10.8% of patients underwent a further WLE, 6.7% underwent a mastectomy at further operation and 1.4% underwent a pathologically avoidable mastectomy or a mastectomy by choice at initial operation.

The rate of pathologically avoidable mastectomy at initial operation was incorporated into the primary end points of this study, as it is possible that MRI may overestimate the size and extent of disease, and thus may inappropriately result in a recommendation for mastectomy. The results showed that 7.1% of patients underwent a mastectomy at initial operation, in the MRI arm. Of these, 16 patients (2.0% of all MRI patients) underwent a pathologically avoidable mastectomy at initial operation, and three patients (0.3% of all MRI patients) underwent a mastectomy through patient choice. As the COMICE trial considers only those women who are already scheduled to receive WLE, identified via triple assessment, it is not possible for us to compare the rate of pathologically avoidable mastectomy as a consequence of triple assessment alone with that for MRI. It is important to note, however, that 39 patients (4.8%) correctly underwent a mastectomy at initial operation, as a result of the MRI findings. Nonetheless, this did not result in a significant reduction in the rate of repeat operation or mastectomy at further operation in this arm.

By considering the effectiveness of MRI alone compared with histopathology, the ability of MRI to correctly identify patients who should undergo a mastectomy was relatively low (sensitivity = 50.0%, 95% CI 42.65 to 57.35; positive predictive value = 61.8%, 95% CI 53.87 to 69.74). The corresponding diagnostic values for triple assessment alone are not available for comparison due to the design of the trial, thus we do not know the true positive rate for mammography and USS.

Influence of surgical expertise

The possible effect of surgical expertise to assimilate and appropriately use the additional information provided by MRI was further investigated by examining the reoperation rates for consultant surgeons who recruited at least the median number of patients recruited per consultant surgeon, and for consultant surgeons who had a reoperation rate of less than 10%, the quality assurance standard for the NHS BSP. We also considered ‘consultant surgeon’ as a categorical variable according to the number of patients

recruited. No statistically significant association between consultant surgeon and reoperation rate was identified for any of these measures; however, there was a trend towards lower reoperation rates for those consultant surgeons with the greatest experience, i.e. those recruiting at least 20 patients. These results would support Department of Health policy, which states that breast surgery should only be carried out by surgeons who perform these operations routinely. Retrospective data from the UK suggest that a minimum caseload of at least 30 newly diagnosed breast cancer cases per consultant per year is required to optimise patient outcomes (level 3 evidence).[77]

No statistically significant association between ACR BI-RADS classification and reoperation rate was identified. However, the patient's age was found to be highly statistically significant, indicating that patients aged 50 years or over were less likely to undergo reoperation than those aged less than 50 (OR 0.64, 95% CI 0.48 to 0.87, $p = 0.0041$). It is important to note, however, that these results may be spurious and should therefore be interpreted with caution. The reasons associated with these findings are unclear. It may be related to the composition/texture of the older breast, which allows for better identification of the tumour separate from the normal surrounding parenchyma, or possibly to the size of the lesions present. Only 7.5% of women aged under 50 had their cancer detected via screening, compared with 65.6% of women aged 50 or over. The median size of the index lesion, as determined via histopathology, was 18 mm (range 4–98 mm) for women aged under 50, and 15 mm (range 0.31–1.5 mm) for women aged 50 or over.

Quality of life issues related with MRI

An extensive QoL analysis was performed, and no significant differences were detected between the trial arms at any of the time points examined.

It proved possible to develop a reliable and acceptable NSSI for use in this population and in this clinical context, and many of the women expressed their appreciation for the opportunity to discuss their experiences with a researcher. The results demonstrated high levels of satisfaction and reassurance in those randomised to receive MRI, despite the reported level of distress secondary to the procedure. Of note, 34% of patients reported significant distress due to feelings of claustrophobia and noise, but this is in accord with previous reports in the literature.[40,41] However, this must be viewed in context: MRI was not the most distressing component of presurgical investigation, as 56% of women found biopsy distressing. As in previous studies, mammography was somewhat less distressing than breast MRI, although 30% indicated that they had found mammography distressing to some extent.

Economic evaluation

The economic analysis of the COMICE trial is consistent with the clinical findings that there is no difference between the trial arms in terms of outcomes. The analysis found that 12 months after initial surgery there was no statistically significant difference in HRQoL, as measured by the EQ-5D, between the arms once baseline HRQoL and several other covariates were controlled for. Although, a small absolute difference was found (0.00088) by the regression, EQ-5D scores are normally only computed to three decimal places. As no clinical differences were observed between the arms in the trial in terms of survival or cancer recurrence, it was felt that a within trial quality-adjusted life-year (QALY) analysis would not be appropriate. Given the nature of the interventions being evaluated and the lack of clinical differences between them, there is no rationale for HRQoL being systematically different between the arms. This is reflected empirically as the EQ-5D scores at all points were very similar. Therefore, any differences in observed QALY scores are likely merely to reflect random noise and their calculation could prove misleading.

A similar logic has been applied to long-term estimates of cost-effectiveness. Given the absence of any short-term clinical differences in the trial (notably cancer recurrence and survival), there is no rationale for extrapolating benefits into the future.

In terms of total costs, the economic analysis did suggest that there may be a difference between the two trial arms with the MRI arm having a larger resource cost. However, after controlling for other covariates, the difference was not found to be statistically significant at a 5% significance level.

Given the similar outcomes of the patients in the two arms, in terms of both clinical outcomes and HRQoL, it can be concluded that the addition of MRI to the conventional triple assessment may result in extra resource use at the initial surgery period with few or no benefits in terms of resource saving or health outcomes resulting from it. The

study gives estimates of the effects of recurrence on costs and EQ-5D scores, which may be useful for other studies, in particular any future modelling studies on a similar patient group.

It is appropriate to comment on some aspects of the methodology of the economic evaluation. Firstly, the large amount of missing data meant that to make efficient use of the data available multiple ICE was used. ICE is based on the assumption that the data are missing at random, and this may not be the case. However, the other alternative approach that could have been undertaken, a complete case analysis, would result in even more data being omitted from the analyses and requires the even stronger assumption that data are missing completely at random.

Secondly, the regression analysis on EQ-5D scores was conducted using ordinary least squares (OLS). OLS may not be fully appropriate for the analysis of such scores as a result of them having upper and lower bounds. However, there is no other validated and accepted approach to analysing such data. The observed EQ-5D scores are significantly different from 1 and the upper bounds of the 95% CIs are also distant from 1, suggesting that the possibility of predictions over 1 is low. It should also be noted that published regression work on EQ-5D scores tends to focus on OLS, indicating that our analysis is generally in line with the approaches taken elsewhere. Finally, the costs and EQ-5D scores have not been combined by a cost-per-QALY analysis. However, the reasons why QALYs have not been calculated have been discussed previously. The results do indicate that the costs in the MRI arm are higher and the health outcomes are very similar, suggesting that the MRI arm is dominated by the no-MRI arm and therefore that the estimation of a cost per QALY would add no further information.

Effectiveness of imaging

In order to consider the effectiveness of MRI compared with mammography and USS, agreement of tumour size, as identified by each of the imaging methods and by histopathology, was considered according to T stage and by considering agreement between methods to within 5 mm. For patients with invasive cancer alone, kappa statistics showed that all imaging methods provide only borderline moderate to fair agreement with histopathology. MR findings were more likely to upstage T1a and b tumours and correctly stage T2 tumours, whereas mammography and USS more frequently correctly staged T1a and b tumours but tended to downstage T2 tumours. The number of stage T3 tumours was inadequate for assessment as might be expected in women scheduled for WLE.

The presence of invasive cancer plus DCIS was separately considered. The agreement between mammography and USS and pathologically determined T stage was found to be lower than that obtained for MRI. The results indicate that USS in particular was poor at detecting lesion size compared with mammography and MRI. Indeed there was virtually no crossover of 95% CI values for MRI and USS. These results were replicated when the agreement between imaging and histopathology to within 5 mm was considered.

Analysis was also performed on the potential factors associated with differences in the size of breast lesion between each of the imaging methods and histopathology. Results showed that patients who were ER positive tended to have the least discrepancy in size between MRI and histopathology, and that the MRI identified larger lesions than pathology for postmenopausal women, although this may be due to shrinkage and orientation effects. The smallest discrepancy between lesion size via mammography and histopathology occurred in patients with ductal NST tumours who were postmenopausal, and in patients who were node positive. Patients who had ductal NST tumours and who were node negative were more likely to have similar tumour sizes identified via USS than histopathology.

In terms of extent of disease, MRI was more likely to agree with histopathology for patients over 50 years of age and patients who have ductal NST tumours. For mammography, extent of disease was more likely to agree with histopathology for patients who were over 50, had ACR BI-RADS group 1, with CIS only or ductal NST and who were node negative, and for USS the extent of disease was more likely to agree with histopathology for patients who had ductal NST tumours and who were node negative. Overall the best agreement between all imaging modalities and histopathology was found in patients who were over 50, had ductal tumours NST and who were node-negative.

Study limitations

Although the sensitivity of MRI for breast cancer is uniformly excellent, with most reports quoting values in excess of 90%, the specificity is poorer ranging between 37% and 90%, but with values

averaging at 85%. In an attempt to maximise specificity and reduce false-positive and false-negative results, the protocol includes both kinetic (functional) and morphological data. The ideal DCE-MRI sequence would provide a temporal resolution of less than 30 seconds to optimally define the signal intensity–time curve; acquire volumetric data sets of both breasts, allowing the use of thinner slices with no interslice gap to minimise partial volume averaging and in-flow effects, preferably with isotropic spatial resolution; and uniform fat suppression throughout the volume of interest. Such stringent technical requirements are not currently feasible at 1.5 T and as a consequence compromises must be made either to the temporal or spatial resolution employed or to extent of the breast coverage obtained. However, with the use of 3.0-T MR systems with parallel imaging, protocols have advanced considerably with a 30-second temporal resolution now possible using an in-plane resolution of 1.0 × 1.0 mm, and a through plane resolution of 2 mm. The improved separation of the fat and water resonances at 3.0 T (180 Hz versus 100 Hz) results in uniform fat signal suppression in virtually all patients. With the introduction of 3.0-T systems in to many of the larger imaging centres within the UK, there is now the option of improving protocols and hence the potential to improve specificity. The addition of high resolution T2-weighted imaging to current T1-weighted sequences may further aid lesion characterisation.

Even with these limitations, the high sensitivity of MRI for breast cancer detection is being increasingly evaluated and applied in the preoperative local staging of breast cancer. A number of studies have reported the capability of MRI in this context, and have shown its ability to identify cancer foci additional to the index lesion, which would have otherwise remained undetected on the basis of clinical assessment and conventional imaging. Although data on MRI detection in this setting have varied between studies, experts have advocated MRI in breast cancer staging on the basis of its detection rate.[78,79] Changes in clinical management following MRI secondary to the detection of abnormalities additional to those found at mammography/USS have been recorded, but at present there is no consensus on whether the use of MRI to detect additional malignant foci within the affected breast improves patient outcome. In this study, 4.8% of women randomised to receive MRI underwent mastectomy, rather than WLE, for undetected multicentric malignancy missed by triple assessment.

Limitations of reference standard for imaging

It is now recognised that the estimated accuracy reported for MRI differs significantly depending on the rigor of the reference standard employed, and is lower for studies with a better quality reference standard. The study by Sardanelli *et al.*,[80] which used lesion-specific histological correlation based on mapping and serial sectioning of mastectomy specimens, reported a lower overall accuracy rate than other studies. An important finding from this study by Sardanelli is that its data on true-positive and false-positive findings did not diverge substantially from other studies, but it reported more false-negative outcomes for MRI than studies that applied a relatively less rigorous radiopathological correlation. Of necessity, the reference standard used in this study was histopathological assessment of mastectomy or WLE specimens and distribution of surgical intervention in all patients. The absence of ipsilateral multifocal or multicentric cancer, or contralateral cancer, was ascertained in women with only localised malignancy (and who did not have mastectomy) by clinical assessment, out to at least 1 year, and by repeat MRI in those with equivocal baseline MR results at 12-month follow-up. This approach was recently used by Lehman and colleagues[81] in a study of the contralateral breast.

We have extensively considered the adequacy of breast imaging employing histopathological measurement of maximum tumour diameter as the reference standard. However, it must be remembered that alterations to tissue dimensions occurring during tissue processing may lead to inaccuracies in measurements. Measuring the shrinkage of cells within tissues suffers not only from the variables introduced by subsequent steps in the processing of tissues, but from other variables such as alterations in the geometry of the block of tissue, as cubes of tissue may have different properties than spheres. In a study performed by Fox *et al.*,[82] in which tissues were fixed in 1.3M formaldehyde solution for 24 hours under time-lapse video photography, strips of rat liver shrank in length by about 3% at room temperature. Subsequent steps in the tissue-processing protocol, alcohol dehydration, clearing in xylene and infiltration with paraffin produced as much as a 20% decrease in the linear dimensions of the tissues, but the amount of shrinkage was depended on the adequacy of the entire fixation sequence.

Pritt *et al.*[83] examined the effect of tissue fixation and processing on breast cancer size from 50

invasive breast tumours. The tumours varied in maximum measured dimension from 4 to 20 mm and contained 10% to 90% estimated fibrous tissue (mean, 52.8%). After final processing and mounting, a decrease in size from initial fresh measurement was noted in 40% of cases (mean difference 2.4 mm; maximum difference, 7 mm), but in nine cases (18%) the measured size increased by a maximum of 3 mm (mean 1.7 mm). Twenty-one cases (42%) showed no change in measurement during the entire fixation and processing protocol. The authors cautioned on the sole reliance on microscopic measurements. In a further study, Yeap and colleagues[84] quantified the shrinkage of breast specimens as a result of formalin fixation. Fifty consecutive mastectomy and wide excision specimens were prospectively appraised, and the closest free margins and maximum tumour diameters of fresh, unprepared specimens were recorded. These measurements were compared with the corresponding parameters following tissue fixation. After formalin fixation, the mean closest free margin of the specimens was found to have decreased from 10.28 mm to 6.78 mm (34%). The reduction of the mean diameter of the tumour itself was less significant, from 41.74 mm to 39.88 mm (4.5%).

Therefore, it is essential that discrepancies in tumour size between histopathology and imaging take account of shrinkage following specimen fixation and processing. In COMICE, the size of index lesion on histopathology was compared with MRI, mammographic and USS measurements. The mean differences in tumour size between histopathology and MRI, mammography and USS were –1.4 mm (SD 10.22), 1.7 mm (SD 10.18) and 4.1 mm (SD 10.21), respectively, with mean tumour diameters of 18.7 mm, 15.6 mm and 13.4 mm for the three imaging modalities compared with 17.5mm for histopathology. The corresponding Pearson correlation coefficients were 0.51, 0.45 and 0.42, respectively, indicating medium correlation between the three imaging methods and histopathology. If one assumes that general breast tumours shrink by an average of 10% from their fresh state then the mean tumour diameter detected by MRI most closely approaches that of histopathology.

Lobular carcinomas and grade III tumours

In COMICE, 9.1% of patients with invasive carcinoma had lobular carcinoma (MRI: 8.5%; no MRI: 9.7%). These women were statistically significantly more likely to undergo a reoperation (OR 0.52, 95% CI 0.30 to 0.92, $p = 0.0242$) than those with alternative histopathology. The correlation between the size of the lobular carcinoma detected by imaging and histopathology varied between modalities, ranging from 0.29 for USS to 0.40 for MRI. Although these results do not translate in to a reduction in reoperation rates, there may be an improvement in the detection of the size of lobular carcinoma present by MRI with respect to USS scanning. These results are in accord with other workers who have found better correlations between MRI and histopathology, than for mammography and USS either alone or in combination.[85] However, given the small number of patients with lobular carcinoma in COMICE these results should be interpreted with caution.

In COMICE, 27.6% of patients had a grade III malignancy (MRI: 26.9%; no MRI: 28.4%). To date we have not correlated tumour grade with maximum tumour diameter or the presence of associated DCIS.

Ductal carcinoma in situ

Only 91 patients in COMICE had DCIS alone, and, as a consequence, little weight can be placed on the results obtained. A larger study focussing on DCIS would be required to fully evaluate the role of MRI with respect to triple assessment in this group of patients.

Limitations of data transfer to surgeons

The results of this study show that the addition of MRI to X-ray mammography and USS does not reduce the reoperation rate. Indeed over the time span of the trial the national reoperation rates reported by the ABS at BASO, for screen detected breast cancer, increased from 14.2% to 17.0%. The NHS BSP relies on X-ray mammography and USS scanning for determination of tumour extent and location, providing one-dimensional data in the former and two-dimensional data by USS with the potential to aid tumour localisation by wire insertion. Despite advances in both imaging modalities, and outwith the context of this trial, reoperation rates have increased.

Surgical techniques for the locoregional treatment of malignancy have changed little since WLE replaced mastectomy as the procedure of choice for tumours of stage II or less. Optimal excision of tumour is now dependent on two factors, namely

the ability of the surgeon to utilise the imaging information provided to correctly determine tumour extent and to palpate the lesion in its entirety during surgery to allow complete excision. This is very demanding considering that all of the imaging modalities acquire information from the patient in a different position to that assumed at surgery; information is variably acquired in one, two or three dimensions, depending on the techniques employed; depending on the composition of the breast, palpation of tumour may be difficult and this may be exaggerated in the presence of minimal infiltration and intraductal extension; and, if wire localisation is employed, typically only one wire is inserted, marking only one point on the circumference of the tumour.

Other surgical specialties, particularly neurosurgery and radiotherapy, increasingly utilise three-dimensional MRI data to localise malignancy and minimise damage to surrounding normal tissue. In these specialties, MRI data is used to direct treatment by referencing the area of abnormality to a surrounding rigid structure or frame, utilising data acquired at a time temporally separate from the acquisition of the imaging data. Utilisation of imaging data in this way is currently not possible for breast surgery.

Generalisability of MRI and comparison with literature

The MRI protocol was pragmatic to allow participation of as many MRI centres within the UK as possible. Both 1.0-T and 1.5-T systems were included if they had a dedicated breast coil for signal reception and were capable of acquiring three-dimensional dynamic contrast-enhanced data of the whole breast with a temporal resolution of 45 seconds, and a through-plane resolution (slice thickness) of 4 mm. This protocol excluded MRI systems without parallel imaging, and, as a consequence of the technical requirements, only two centres operating at 1.0 T participated. High-resolution post-contrast imaging is standard on all systems, but uniform fat suppression throughout the volume of interest can be problematic. Consequently, image subtraction was permitted as an alternative, although it is recognised to be suboptimal when patient movement has occurred between pre- and post-contrast images.

Involvement of 45 radiology departments within the UK inevitably resulted in variable experience in the interpretation of MR breast imaging; however, an independent quality assurance review found good adherence to the protocol overall.

Evidence from a systematic review and meta-analysis of 19 studies based on 2610 patients that examined the detection of multifocal and multicentric breast cancer, showed that MRI detected additional disease in the affected breast in 16% of women with breast cancer.[86] The summary estimate of the positive predictive value was 66% (95% CI 52% to 77%) and true-positive to false-positive ratio was 1.91 (95% CI 1.09 to 3.34). In this study the conversion from WLE to mastectomy was 8.1% (95% CI 5.9 to 11.3), and from WLE to more extensive surgery (wider/additional excision or mastectomy) was 11.3% in patients with multifocal and multicentric disease (95% CI 6.8 to 18.3). In women who had additional lesions detected by MRI and in whom histology did not identify any additional malignancy, conversion from WLE to mastectomy was 1.1% (95% CI 0.3 to 3.6), and from WLE to more extensive surgery was 5.5% (95% CI 3.1 to 9.5). The results reported in COMICE are reflective of the above findings of Houssami,[86] with respect to the positive predictive value and conversion to mastectomy rates, thus reiterating the generalisability of the findings of the COMICE trial. However, the proportion of patients for whom MRI detected additional lesions and histology did not (i.e. change in surgery due to false-positive detection) is much lower in the meta-analysis study reported by Houssami than in COMICE (based upon reasons for change in proposed clinical management) – Houssami 1.1%, COMICE 28.0%.

The systematic review by Houssami *et al.*[86] also showed consistent evidence that MRI staging results in more extensive surgery in an important proportion of women. In women with histologically proven additional foci of cancer detected by MRI, meta-analysis showed that conversion from WLE to more extensive surgery, commonly mastectomy, occurred in 11.3% of instances. While data on detection indicate that many of the false-positive findings are investigated with needle biopsy, these false-positive results still caused histopathologically avoidable conversion to more extensive surgery in 5.5% of women. In COMICE the mean weight of the resected specimens obtained at WLE was only slightly greater in the MRI arm, at 70.55 g (SD 54.63) compared with 63.69 g (SD 52.11) for the no-MRI arm, the median values were similar at 54 g (range 5.93–95.0) and 51 g (range 5.07–70.0) for the MRI and no-MRI arms, respectively. Thus,

in patients who underwent WLE as planned, there was no difference in the volume of tissue resected between the trial arms.

Summary

The results of the COMICE trial are important from both a health economic aspect, and also from a patient burden aspect. MRI is an expensive procedure. The findings of this trial are of benefit to the NHS as they show that this additional procedure may not be necessary in this population of patients, thus additional funding may not required and potential increases in waiting lists for MRI may be avoided. Furthermore, not requiring an MR scan may relieve the burden of an additional hospital visit or a delay in the care pathway due to the availability of an MRI slot.

The COMICE study is the first large pragmatic trial evaluating the effectiveness of MRI of small breast lesions, suitable for WLE. The results have shown that the addition of MRI to triple assessment in women with breast tumours deemed suitable for treatment by WLE does not result in a reduction in the subsequent reoperation rates. However, this does not necessarily reflect a poor correlation between tumour extent as assessed by MRI and histopathology. This correlation is in general better than that obtained for mammography and USS, particularly for larger lesions and although the kappa statistic is only in the fair to moderate range, allowance must be made for inaccuracies in histopathological reference measurements, due to the orientation of sectioning of tissue blocks and the inability to correct for tissue shrinkage that occurs during processing and mounting. As detection of intraductal tumour is limited macroscopically, use of fresh specimens would not have been a feasible alternative. The improved sensitivity of MRI over mammography and USS is reflected in the detection of increased lesion size or multifocal/multicentric disease in 39 women, who following MRI underwent mastectomy appropriately.

A small percentage of patients underwent a pathologically avoidable mastectomy due to the suboptimal specificity of MRI, emphasising the requirement for biopsy of lesions that might result in an alteration to the planned surgical procedure.

The extensive QoL analysis performed showed no differences between the trial arms. It demonstrated high levels of satisfaction and reassurance in those randomised to receive MRI, despite the reported levels of distress secondary to the procedure, which were comparable to those reported for mammography and less than those for breast biopsy.

Several studies have examined the importance of tumour-free surgical margins after breast-conserving therapy.[3–6] Ideally, the tumour, along with a margin of at least 10 mm of normal-appearing tissue, is resected to attempt to remove any microscopic cancer. The minimum cosmetically acceptable tumour-free margin in relation to the risk of local or distant recurrence has been debated in many studies.[87,88] For image-guided ablation successful treatment of the entire tumour relies on accurate tumour volume delineation using imaging for both tumours targeting and monitoring the ablation procedure. Although the results of COMICE did not result in a reduction in the reoperation rate, there was a fair to moderate correlation of imaging with histopathology. The audit of the NHS BSP by ABS at BASO also indicates that, at best, there has been no reduction in the reoperation rate following WLE over the past 7 years. This is despite advances in imaging techniques and an experienced workforce. Thus, considerations must be given to the investigation of alternative treatments, potentially image-guided ablation, for the treatment of small tumours.

Implications for practice

The addition of MRI to triple assessment in women with small breast tumours does not result in a reduction in reoperation rates.

Preoperative biopsy of MRI-only-detected lesions prior to surgery is likely to minimise the incidence of inappropriate mastectomy.

Research recommendations

Improved specificity of MRI

It is hoped that an improvement in specificity can be realised at 1.5 T, but technical limitations remain at this field strength. Additionally, the underlying new vessel formation inherent with some benign as well as malignant processes, particularly those giving rise to diffuse abnormalities, may remain problematic. In view of the issues relating to specificity, it is important to reiterate the

requirement for biopsy of lesions, which may significantly alter surgical management and result in more extensive surgery than is required.

Presentation of imaging data for surgical management

The mode of presentation of imaging data for optimal surgical management should be further examined, together with the issues surrounding the mark-up of tumour extent prior to resection.

Use of higher field MRI systems

The introduction of 3.0-T MR systems offers significant improvements in breast imaging. Although relatively recently introduced, these systems are gaining increasing interest nationally and there is a growing installed base. MRI at 3.0 T provides, approximately, a twofold increase in signal–noise ratio, compared with 1.5-T systems. This allows the implementation of parallel imaging techniques with the inherent reduction in signal-to-noise ratio that is implicit in their use. By employing these techniques, three-dimensional acquisition of both breasts is obtainable at 3.0 T with a temporal resolution of approximately 15 seconds, allowing pharmacokinetic modelling to be undertaken.

The greater separation of the resonant frequencies of water and fat at 3.0 T, compared to 1.5 T, is used to good effect in chemical shift-specific, fat suppression techniques, providing uniform fat suppression. High spatial resolution using both T1- and T2-weighted sequences provides greater morphological detail than is currently obtainable at 1.5 T and potentially will result in greater specificity.

Alternative treatment options

It is now recognised that more extensive surgery may have little long-term clinical benefit, as residual disease may be adequately treated with standard adjuvant therapy. As the volume of tissue excised in breast-conserving surgery is the single most important factor predicting cosmetic outcome, the potential harm of removing more breast tissue than is necessary has significant implications. Indeed, there is now a trend to accept 'close' surgical margins, which may only be 1–2 mm in thickness, rather than insist on a 1 cm margin. With current adjuvant therapy the rate of development of recurrent cancer in a treated breast over time is also small.

The cosmetic outcome of breast-conserving surgery is often suboptimal, due to the resection of a 1 cm margin of normal breast tissue around the tumour and the use of postoperative radiation. Technological advances over the last decade have fuelled interest in even less invasive treatment of patients with localised breast cancer, using techniques that are image-guided to ensure accurate tumour localisation. Currently available minimally invasive image-guided tumour ablation techniques include radiofrequency ablation, cryoablation, laser ablation, microwave ablation and focused USS ablation.[89]

Acknowledgements

The trial would not have been possible without the valued contributions of the women who were willing to participate in the study.

We would like to thank the following for their hard work in the conduct of this trial: all surgeons, radiologists, radiographers, research nurses, data managers and pathologists involved in the study at the participating centres.

We would also like to acknowledge all members of the Trial Steering Committee (Appendix 1), Data Monitoring and Ethics Committee (Appendix 4) and Trial Management Group (Appendix 3).

Clinical Trials Research Unit, University of Leeds

Trial Statisticians: Julia Brown, CTRU Director; Sarah Brown, Senior Medical Statistician.

Trial Coordination Team: Vicky Napp, Operations Director; Catherine Olivier, Senior Trial Manager.

And all additional CTRU staff, past and present, who have contributed to the COMICE trial (trial co-ordination, statistics, data entry and administration, database development and support).

Centre for Health Economics, University of York

Andrea Manca, Senior Research Fellow; Mark Sculpher, Professor of Health Economics; and Simon Walker, Research Fellow

The NSSI (Well-Being) Study – Institute of Rehabilitation, University of Hull

Donald Sharp, Senior Lecturer in Behavioural Oncology; Mike Mooney, Research Assistant; Leslie Walker, Director of Institute of Rehabilitation.

Participating centres

The following centres and Principal Investigators contributed patients to the trial: Barnet Hospital, Dr G Kaplan; Blackpool Victoria Hospital, Dr G Hoadley; Bristol Royal Infirmary, Dr A Jones; Castle Hill Hospital, Hull, Professor L Turnbull; Conquest Hospital, Hastings, Miss E Shah; Crosshouse Hospital, Ayrshire, Dr M Dean; Darent Valley Hospital, Kent, Dr Bashir Al-Murrani; Derriford Hospital, Plymouth, Dr K Paisley; Diana Princess of Wales Hospital, Grimsby Mr LA Donaldson; Frenchay Hospital, Bristol, Mr S Cawthorn; George Eliot, Nuneaton, Mr R Nangalia; Grantham and District Hospital, Mr D Valerio; Hairmyres Hospital, East Kilbride Dr D Edwards; Hillingdon, Dr K Raza; Hinchingbrooke Hospital, Huntingdon, Dr C Hubbard; Hope Hospital, Salford, Dr S Datta; King's College Hospital, London, Dr D Evans; Leeds General Infirmary, Dr B Dall; Leighton Hospital, Chester, Dr S Evans; Luton & Dunstable Hospital, Dr D Wright; Maidstone Hospital, Dr A Sever; Mid Yorkshire Hospitals NHS Trust (Clayton Hospital, Dewsbury and District Hospital, Pinderfields General Hospital, Pontefract General Infirmary), Dr F Roberts; Northwick Park, Harrow, Dr W Teh; Nottingham City Hospital, Dr J James; Prince Philip Hospital, Carmarthenshire, Mr A Richards; Princess of Wales, Bridgend, Dr N Al-Mokhtar; Rotherham General Hospital, Dr S Varkey; Royal Bolton Hospital, Mr JHR Winstanley; Royal Hallamshire Hospital, Sheffield, Dr C Ingram; Royal Lancaster Infirmary, Mr J Lavelle; Royal Sussex County Hospital, Brighton, Dr G Rubin; Russells Hall Hospital, Dudley, Dr H Renny; Scarborough Hospital, Mr J Macfie; St Bartholomew's Hospital, London, Dr S Vinnicombe; St James's University Hospital, Leeds, Mr M Lansdown; St Mary's Hospital, London, Dr W Gedroyc; University Hospital of North Durham, Dr Julie Cox; University Hospital of North Tees Hospital, Mr Hennessy; Victoria Infirmary, Glasgow, Miss S Stallard; Walsgrave Hospital, Coventry, Dr M Wallis; Western General Hospital,

Edinburgh, Mr J Rainey; Western Infirmary, Glasgow, Dr L Wilkinson; Whiston Hospital, Prescot, Mr R Audisio; York Hospital, Dr S Reaney; Ysbyty Gwynedd, Bangor, Professor NSA Stuart.

Contribution of authors

Professor Lindsay Turnbull, (Centre for MR Investigations, University of Hull) was Chief Investigator for the trial, a grant co-applicant who contributed to the conception, design, conduct and monitoring of the trial, and who contributed to the analysis, the interpretation of results, the drafting of the report and approved the final version.

Sarah Brown (Senior Medical Statistician, Clinical Trials Research Unit, University of Leeds) conducted the analysis of the clinical data, participated in the data monitoring, interpretation of results, contributed to the drafting of the report and approved the final version.

Catherine Olivier (Senior Trial Manager, Clinical Trials Research Unit, University of Leeds) contributed to the conduct of the trial, was instrumental in collection and verification of all data, participated in the interpretation of results, the drafting of the report and approved the final version.

Dr Ian Harvey (COMICE Project co-ordinator, University of Hull) led the quality assurance review, participated in centre enrolment, data monitoring, contributed to the drafting of the report and approved the final version.

Professor Julia Brown (Director, Clinical Trials Research Unit, University of Leeds) was the Supervising Statistician for the trial, and took a lead role in protocol development and implementation, contributed to data monitoring, the analysis, interpreting the data and approving the final version of the report.

Professor Phil Drew (Honorary Consultant Surgeon, Royal Cornwall Hospitals NHS Trust), a grant co-applicant who contributed to the design of the trial, participated in the data collection, data monitoring, the interpretation of results, contributed to the drafting of the report and approved the final version.

Professor Andy Hanby contributed to the design of the trial, data collection, data monitoring, contributed to the drafting of the report and approved the final version.

Andrea Manca (Senior Research Fellow, Centre for Health Economics, University of York) contributed to the design of the trial and oversaw the economic evaluation, and contributed to drafting sections of the report describing the methods and results of the economic evaluation analysis, and approved the final version of the report.

Vicky Napp (Operations Director, Clinical Trials Research Unit, University of Leeds) who was CTRU Principal Investigator for the project, contributed to the design of the trial, trial set-up, the conduct of the trial, chaired meetings on a regular basis to review and manage the progress of the project, contributed to analysis and approved the final version of the report.

Professor Mark Sculpher (Professor of Health Economics, Centre for Health Economics, University of York) was a grant co-applicant who contributed to the design of the trial and oversaw the economic evaluation, and contributed to drafting sections of the report describing the methods and results of the economic evaluation analysis, and approved the final version of the report.

Professor Leslie Walker (Director of Institute of Rehabilitation, University of Hull) was a grant co-applicant and was the lead for the NSSI (Well-Being) Sub-Study contributing to the design of the trial, data monitoring, interpretation of Quality of Life results, drafting of the report and approved the final version.

Simon Walker (Research Fellow, Centre for Health Economics, University of York) conducted the economic evaluation analysis and interpretation of results, contributed to drafting sections of the report describing the economic evaluation analysis, and approved the final version of the report.

References

1. Del Turco MR, Mantellini P, Ciatto S, Bonardi R, Martinelli F, Lazzari B, *et al.* Full-field digital versus screen-film mammography: comparative accuracy in concurrent screening cohorts. *AJR* 2007;**4**:860–6.

2. Kaplan E, Yu E, Tripathy D. MRI patterns predict ability to perform breast conservation following neoadjuvant therapy for locally advanced breast cancer. *Breast Cancer Res Treatment* 2003;**82**(Suppl.):1–9.

3. Park CC, Mitsumori M, Nixon A, Recht A, Connolly J, Gelman R, *et al.* Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol* 2000;**18**:1668–75.

4. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, *et al.* The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med* 1999;**340**:1455–61.

5. Singletary SE. Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg* 2002;**184**:383–93.

6. Tartter PI, Kaplan J, Bleiweiss I, Gajdos C, Kong A, Ahmed S, *et al.* Lumpectomy margins, reexcision, and local recurrence of breast cancer. *Am J Surg* 2000;**179**:81–5.

7. Van Goethem M, Schelfout K, Dijckmans L, Van Der Auwera JC, Weyler J, Verslegers I, *et al.* MR mammography in the pre-operative staging of breast cancer in patients with dense breast tissue: comparison with mammography and ultrasound. *Eur Radiol* 2004;**14**:8091–6.

8. Mariani L, Salvadori B, Marubini E, Conti AR, Rovini D, Cusumano F, *et al.* Ten year results of a randomised trial comparing two conservative treatment strategies for small size breast cancer. *Eur J Cancer* 1998;**34**:1156–62.

9. Guinot JL, Roldan S, Maronas M, Tortajada I, Carrascosa M, Chust ML, *et al.* Breast-conservative surgery with close or positive margins: can the breast be preserved with high-dose-rate brachytherapy boost? *Int J Radiation Oncol Biol Phys* 2007;**68**:1381–7.

10. Karasawa K, Mitsumori M, Yamauchi C, Gomi K, Kataoka M, Uematsu T, *et al.* Treatment outcome of breast-conserving therapy in patients with positive or close resection margins: Japanese multi institute survey for radiation dose effect. *Breast Cancer* 2005;**12**:91–8.

11. Ramanah R, Pivot X, Sautiere JL, Maillet R, Riethmuller D. Predictors of re-excision for positive or close margins in breast-conservation therapy for pT1 tumors. *Am J Surg* 2008;**195**:770–4.

12. Zavagno G, Goldin E, Mencarelli R, Capitanio G, Del BP, Marconato R, *et al.* Role of resection margins in patients treated with breast conservation surgery. *Cancer* 2008; 112:1923–31.

13. NHS Breast Screening Programme and the Association of Breast Surgery. An audit of screen detected breast cancer for year of screening April 2006 to March 2007. Association of Breast Surgery at BASO conference, Birmingham, 11 June 2008.

14. Palka I, Kelemen G, Ormandi K, Lazar G, Nyari T, Thuro L, *et al.* Tumour characteristics in screen-detected and symptomatic cancers. *Pathol Oncol Res* 2008;**14**:161–7.

15. Harms SE, Flamig DP, Hesley KL, Meiches MD, Jensen RA, Evans WP, *et al.* MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. *Radiology* 1993;**187**:493–501.

16. Davies PL, Staiger MJ, Harris KB, Ganott MA, Klementaviciene J, McCarthy KS, *et al.* Breast cancer measurements with magnetic resonance imaging, ultrasound and mammography. *Breast Cancer Res Treatment* 1996;**37**:1–9.

17. Ando Y, Fukatsu H, Ishigaki T, Endo T, Mikazaki M. Evaluation of breast cancer vascularity using MR mammography. In: *Proceedings of the 5th ISMRM Meeting*, Vancouver, Abstract 1045; April 1997.

18. Boetes C, Mus RD, Holland R, Barentsz JO, Strijk SP, Wobbes T, *et al.* Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent. *Radiology* 1995;**197**:743–7.

19. Hata T, Takahashi H, Watanabe K, Takahashi M, Taguchi K, Itoh T, *et al.* Magnetic resonance imaging for preoperative evaluation of breast cancer: a comparative study with mammography and ultrasonography. J Am Coll Surg 2004;**198**:190–7.

20. Brix G, Schreiber W, Hoffmann U, Guckel F, Hawighorst H, Knopp MV. [Methodological approaches to quantitative evaluation of microcirculation in tissues with dynamic magnetic resonance tomography.] [German]. *Radiologe* 1997;**37**:470–80.

21. Knopp MV, Weiss E, Sinn HP, Mattern J, Junkermann H, Radeleff J, *et al.* Pathophysiologic basis of contrast enhancement in breast tumors. *J Magn Reson Imaging* 1999;**10**:260–6.

22. Tofts PS, Berkowitz BA. Measurement of capillary permeability from the Gd enhancement curve: a comparison of bolus and constant infusion injection methods. *J Magn Reson Imaging* 1994;**12**:81–91.

23. American College of Radiology. *Breast imaging reporting and data system atlas* (*BI-RADS atlas)*. Reston, VA: American College of Radiology; 2003.

24. Kuhl CK, Schild HH, Morakkabati N. Dynamic bilateral contrast-enhanced MR imaging of the breast: trade-off between spatial and temporal resolution. *Radiology* 2005;**236**:789–800.

25. Goto M, Ito H, Akazawa K, Kubota T, Kizu O, Yamada K, *et al.* Diagnosis of breast tumors by contrast-enhanced MR imaging: comparison between the diagnostic performance of dynamic enhancement patterns and morphologic features. *J Magn Reson Imaging* 2007;**25**:104–12.

26. Gibbs P, Liney GP, Lowry M, Kneeshaw PJ, Turnbull LW. Differentiation of benign and malignant sub-1 cm breast lesions using dynamic contrast enhanced MRI. *Breast* 2004;**13**:115–21.

27. Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, *et al.* Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* 2005;**365**:1769–78.

28. Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, *et al.* Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* 2005;**23**:8469–76.

29. Trecate G, Vergnaghi D, Manoukian S, Bergonzi S, Scaperrotta G, Marchesini M, *et al.* MRI in the early detection of breast cancer in women with high genetic risk. *Tumori* 2006;**92**:517–23.

30. Kneeshaw PJ, Lowry M, Manton D, Hubbard A, Drew PJ, Turnbull LW. Differentiation of benign from malignant breast disease associated with screening detected microcalcifications using dynamic contrast enhanced magnetic resonance imaging [see comment]. *Breast* 2006;**15**:293–8.

31. Bazzocchi M, Zuiani C, Panizza P, Del FC, Soldano F, Isola M, *et al.* Contrast-enhanced breast MRI in patients with suspicious microcalcifications on mammography: results of a multicenter trial. *AJR* 2006;**6**:1723–32.

32. Kramer S, Schulz-Wendtland R, Hagedorn K, *et al*. Magnetic resonance imaging and its role in the diagnosis of multicentric breast cancer. *Anticancer Res* 1998;**18**:2163–4.

33. Balen FG, Hall-Craggs MA, Mumtaz H, Wilkinson I, Scheidau A. MRI of invasive lobular carcinoma of the breast. *Proceedings of Radiology 1997*, Birmingham, 19–21 May, p. 51. *Br J Radiol* 1997; **40**(Suppl.).

34. Tan JE, Orel SG, Schnall MD, Schultz DJ, Solin LJ. Role of magnetic resonance imaging and magnetic resonance imaging: guided surgery in the evaluation of patients with early-stage breast cancer for breast conservation treatment. *Am J Clin Oncol* 1999;**22**:414–8.

35. Fischer U, Kopka L, Grabbe E. Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. *Radiology* 1999;**213**:881–8.

36. Gilbert FJ, Cordiner CM, Affleck IR, Hood DB, Mathieson D, Walker LG. Breast screening: the psychological sequelae of false-positive recall in women with and without a family history of breast cancer. *Eur J Cancer* 1998;**34**:2010–14.

37. Sutton S, Saidi G, Bickler G, Hunter J. Does routine screening for breast cancer raise anxiety? Results from a three wave prospective study in England. *J Epidemiol Community Health* 1995;**49**:413–18.

38. Cockburn J, Staples M, Hurley SF, De LT. Psychological consequences of screening mammography. *J Med Screening* 1994;**1**:71–2.

39. Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A. Psychological side effects of breast cancer screening. *Health Psychol* 1991;**10**:259–67.

40. Anderson J, Walker LG. Psychological aspects of MRI breast screening in women at high risk of breast cancer. In Warren RM, Coultard A, editors. *Breast MRI in practice*. London: Martin Dunitz; 2002.

41. Anderson J, Walker LG, Leach MO. Magnetic resonance imaging: an acceptable way of screening women with a family history of breast cancer. 27th Annual San Antonio Breast Cancer Symposium, 2004, p. 5014.

42. Brown J, Coulthard A, Dixon AK, Dixon JM, Easton DF, Eeles RA, *et al.* Rationale for a National Multi-Centre Study of Magnetic Resonance Imaging (MRI) Screening in Women at Genetic Risk of Breast Cancer. *Breast* 2000;**9**:72–7.

43. Brown J, Coulthard A, Dixon AK, Dixon JM, Easton DF, Eeles RA, *et al.* Protocol for magnetic resonance imaging screening in women at high genetic risk of breast cancer. *Breast* 2000;**9**:78–82.

44. van DS, Seynaeve C, Rijnsburger AJ, Duivenvoorden HJ, Essink-Bot ML, Tilanus-Linthorst MM, *et al.* Exploring the course of psychological distress around two successive control visits in women at hereditary risk of breast cancer. *Eur J Cancer* 2005;**41**:1416–25.

45. Watson EK, Henderson BJ, Brett J, Bankhead C, Austoker J. The psychological impact of mammographic screening on women with a family history of breast cancer: a systematic review [review; 26 refs]. *Psycho-Oncology* 2005;**14**:939–48.

46. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.

47. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, *et al.* Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol* 1997;**15**:974–86.

48. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, *et al.* The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9.

49. Brown GW, Rutter M. The measurement of family activities: a methodological study. *Hum Relations* 1966;**19**:241–63.

50. Walker LG, McKay E, Booth M, Crawford D, Davidson MI, Hunter D, *et al. Multi-disciplinary assessment of pre-school handicapped children*: *pathways, professionals and parents*. Aberdeen: University of Aberdeen; 1987.

51. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, *et al.* Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System. *J Clin Oncol* 2007;**25**:2127–32.

52. Berg WA, Gilbreath PL. Multicentric and multifocal cancer: whole-breast US in preoperative evaluation. *Radiology* 2000;**214**:59–66.

53. Allen MJ, Thompson WD, Stuart RC, Gill PT, Walton EW, Karczenski K, *et al.* Management of non-palpable breast lesions detected mammographically. *Br J Surg* 1994;**81**:543–5.

54. Egan JF, Sayler CB, Goodman MJ. A technique for localizing occult breast lesions. *CA Cancer J Clin* 1976;**26**:32–7.

55. Norton LW, Zeligman BE, Pearlman NW. Accuracy and cost of needle localization breast biopsy. *Arch Surg* 1988;**123**:947–50.

56. Hermann G, Janus C, Lesnick G. Percutaneous localization of nonpalpable breast lesions. *Breast* 1983;**1**:4–6.

57. Jackman RJ, Marzoni FA, Jr. Needle-localized breast biopsy: why do we fail? *Radiology* 1997;**204**:677–84.

58. Fischer U, von HD, Vosshenrich R, Vieweg I, Grabbe E. [Signal characteristics of malignant and benign lesions in dynamic 2D-MRT of the breast] [German]. *ROFO Fortschr Geb Rontgenstr Nuklearmed* 1993;**158**:287–92.

59. Kaiser WA, Zeitler E. MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Preliminary observations. *Radiology* 1989;**170**:681–6.

60. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, *et al.* Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiology* 1999;**211**:101–10.

61. Euroqol webpage. URL: www euroqol org/ 2008

62. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990;**16**:199–208.

63. Kind P. *The EuroQoL instrument*: *an index of health-related quality of life. Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia: Lippincott-Raven; 1996.

64. Medical Research Council. *MRC guidelines for good clinical practice in clinical trials*. London: MRC; 1998.

65. BASO. An audit of screen detected breast cancer for year of screening April 1998 to May 1999. BASO Specialist Group Meeting, 2000. Included in the following report: www.cancerscreening.nhs.uk/breastscreen/publications/baso2003–2004.pdf.

66. Drummond MF, Sculpher MJ, O'Briend BJ, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford Medical Publications; 2005.

67. Department of Health. NHS reference costs 2006–7. London: HMSO; 2006.

68. British Medical Association, The Royal Pharmaceutical Society of Great Britain. *British National Formulary*. URL: www BNF org 2007

69. Curtis L. *Unit costs of health and social care 2007*. Personal Social Services Research Unit, University of Kent; 2007.

70. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQol*: *results from a UK general population survey*. York: University of York, Centre for Health Economics; 1995.

71. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Services Res Policy* 2004;**9**:197–204.

72. Royston P. Multiple imputation of missing values. *Stat J* 2004;**4**:227–41.

73. Moher D, Schulz KF, Altman D, CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;**285**:1987–91.

74. Kirkwood BR, Sterne JAC. Measurement error: assessment and implications. In *Essential Medical Statistics*. 2nd edn. Oxford: Blackwell Science; 2003, pp. 429–46.

75. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;**1**:79.

76. Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, *et al.* A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. *J Clin Epidemiol* 2004;**57**:898–910.

77. Association of Breast Surgery @ BASO RCoSoE. Guidelines for the management of symptomatic breast disease. *Eur J Surg Oncol* 2005;**31**(Suppl. 1):1–21.

78. Liberman L. Breast MR imaging in assessing extent of disease [review; 54 refs]. *Magn Reson Imaging Clin N Am* 2006;**14**:339–49.

79. Smith RA. The evolving role of MRI in the detection and evaluation of breast cancer [comment]. *N Engl J Med* 2007;**356**:1362–4.

80. 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* 2004;**183**:1149–57.

81. 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;**356**:1295–303.

82. Fox CH, Johnson FB, Whiting J, Roller PP. Formaldehyde fixation. *J Histochem Cytochem* 1985;**33**:845–53.

83. Pritt B, Tessitore JJ, Weaver DL, Blaszyk H. The effect of tissue fixation and processing on breast cancer size. *Human Pathol* 2005;**36**:756–60.

84. Yeap BH, Muniandy S, Lee SK, Sabaratnam S, Singh M. Specimen shrinkage and its influence on margin assessment in breast cancer. *Asian J Surg* 2007;**30**:183–7.

85. Kneeshaw PJ, Turnbull LW, Drew PJ. Role of magnetic resonance imaging in the diagnosis and single-stage surgical resection of invasive lobular carcinoma of the breast (*Br J Surg* 2002;**89**:1296–1301) [comment]. *Br J Surg* 2003;**90**:248.

86. 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;**38**:419–25.

87. Montgomery DA, Krupa K, Jack WJ, Kerr GR, Kunkler IH, Thomas J, *et al.* Changing pattern of the detection of locoregional relapse in breast cancer: the Edinburgh experience. *Br J Cancer* 2007;**96**:1802–7.

88. Morrow M, Freedman G. A clinical oncology perspective on the use of breast MR. *Magn Reson Imaging Clin N Am* 2006;**14**:363–78.

89. Schmitz AC, Gianfelice D, Daniel BL, Th WP, van den Bosch MAAJ. Image-guided focused ultrasound ablation of breast cancer: current status and future directions. *Eur Radiol* 2008;**18**:1431–41.

90. NHS Cancer Screening Programmes and the Royal College of Pathologists. *Pathology reporting of breast disease*. Report no. 58. London: Department of Health; 2005.

91. Culyer AJ, McCabe C, Briggs A, Claxton K, Burton M, Akehurst R, *et al.* Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. *J Health Services Res Policy* 2007;**12**:56–8.

92. NICE. *Guide to the methods of technology appraisal*. London: NICE, 2008.

Appendix 1

COMICE Trial Steering Committee

Independent members

Dr David Dodwell, Consultant Oncologist, Bexley Wing, St James's Institute of Oncology, St James's University Hospital, Beckett St, Leeds, LS9 7TF

Professor Tom Lennard, Head of School of Surgical & Reproductive Sciences, The Medical School, William Leech Building, Framlington Place, University of Newcastle, Newcastle upon Tyne, NE2 4HH

Dr Robert Newcombe, Senior Lecturer in Medical Statistics, Dept. of Mathematics, University of Wales, College of Medicine, Heath Park, Cardiff, CF14 4XN

Professor Jon Nicholl (Chair), Medical Care Research Unit, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Mrs Liz Thrustle-Webster, Consumer Representative

Advisor

Mr Hugh Bishop, Consultant Surgeon, Royal Bolton Hospital, Minerva Road, Farnworth, Bolton, BL4 0JR

Appendix 2

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 3

COMICE Trial Management Group

Professor Lindsay Turnbull (Chief Investigator), Professor of Radiology, Centre for MR Investigations, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ

Dr Barbara Dall, Consultant Radiologist in Breast Imaging, Department of Radiology, Leeds United Teaching Hospitals, Wharfedale General Hospital, Newall Carr Rd, Otley, W Yorks, LS21 2LY

Professor Phil Drew, Professor/Honorary Consultant Surgeon, Royal Cornwall Hospitals NHS Trust, The Royal Cornwall Hospital, Truro, TR1 3LJ

Professor Andrew Hanby, Chair of Breast Pathology, Dept. of Pathology, Leeds Teaching Hospitals Trust, St James's University Hospital, Beckett St, Leeds, LS9 7TF

Dr Ian Harvey, Project Co-ordinator, Centre for MR Investigations, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ

Professor Leslie G Walker, Chair of Cancer Rehabilitation, and Clinical Lead, Division of Cancer, University of Hull, Director, Institute of Rehabilitation and Oncology Health Centres, University of Hull and Hull and East Yorkshire Hospitals NHS Trust, Institute of Rehabilitation, 215 Anlaby Rd, Kingston upon Hull, East Riding of Yorkshire, HU3 2PG, UK

Clinical Trials Research Unit (CTRU: University of Leeds, Clinical Trials Research House, 717–5 Clarendon Road, Leeds, LS2 9PH)

Professor Julia Brown, CTRU Director

Mrs Sarah Brown, Senior Medical Statistician

Miss Vicky Napp, Operations Director (CTRU PI)

Miss Catherine Olivier, Senior Trial Manager

Centre for Health Economics (University of York, Heslington, York, YO10 5DD)

Mr Andrea Manca, Senior Research Fellow

Professor Mark Sculpher, Professor of Health Economics

Simon Walker, Research Fellow

Appendix 4

COMICE Data Monitoring and Ethics Committee

Professor Marion Campbell, Director, Health Service Research Unit, University of Aberdeen Medical School, Drew Kay Wing, Foresterhill, Aberdeen, AB25 9ZD

Mr Alastair Paterson , Consultant Surgeon, Royal Cornwall Hospital, Treliske, Truro, TR1 3LJ

Dr Sarah Pinder, Professor of Breast Pathology, Department of Academic Oncology, 3rd Floor Thomas Guy House, Guy's Hospital, St Thomas Street, London, SE1 9RT

Dr Ruth Warren, Consultant Radiologist, Addenbrookes Hospital, Hills Road, Cambridge, CB2 2QQ

Previous members

Dr Andrew J Evans, Consultant Radiologist, Nottingham International Breast Education Centre, City Hospital, Hucknall Road, Nottingham, NG5 1PB

Mr Richard Rainsbury, Consultant Breast Surgeon, Royal Hampshire County Hospital, Romsey Road, Winchester, SO22 5DG

Dr Clive Wells, Consultant in Pathology, Department of Pathology, St Bartholomews Hospital, West Smithfield, London, EC1A 7BE

Appendix 5

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 6

Patient information sheet

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 and 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. We will also hold a copy of your signed consent form.

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 four short questionnaires at baseline, 8 weeks after randomisation, and 6 months and 12 months after your operation to find out how you feel. 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 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 Multicentre 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 7

Patient consent form

(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 8

Details of clinical data and health service resource use data collection

Clinical data

Initial clinical details

The research nurse collected 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 consultant breast surgeon
- date of diagnosis
- dates of mammography and USS
- use of preoperative neoadjuvant therapy.

Mammographic and USS findings

The reporting radiologist recorded 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.

Magnetic resonance imaging findings

THE reporting radiologist recorded the following data:

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

Patient management

Following MRI, the surgical management was reviewed by the multidisciplinary team at each recruiting centre. A change to the proposed surgical management was recorded by the named consultant breast surgeon as either:

- no action
- conversion to mastectomy
- conversion to primary chemotherapy.

Surgery

The following information was collected by the surgeon:

- dates of admission/surgery
- type of operation
- intraoperative complications and their management, including fluid replacement, analgesia, antibiotics and need for blood transfusion.
- length of time in theatre/anaesthetic time
- length of operation and axillary procedure (if applicable).

Histopathology from initial surgery

Following weighing, serial sectioning of appropriately marked excised specimens (WLE or mastectomy) was carried out with reference to the MRI hard copy and in accordance with the guidelines in the NHS BSP publication 'Pathology reporting in breast cancer screening'.[90] 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 was collected. The following additional information was collected:

- size and malignancy of index and additional (multifocal and/or multicentric) lesions
- distance between index and other lesions
- number of blocks taken.

Postoperative information

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

- date of discharge
- postoperative complications and their management, including fluid replacement, analgesia, antibiotics, need for blood transfusion, etc.

Follow-up

Patients were followed up for a maximum of 5 years. The following information was recorded.

At 6 months

- Readmissions to hospital including reasons and dates.
- Complications due to surgery.
- Whether the patient had repeat surgery/ mastectomy.
- Dates of admission/surgery.
- Type of operation.
- Intraoperative complications and their management, including fluid replacement, analgesia, antibiotics, need for blood transfusion, etc.
- Length of time in theatre/anaesthetic time.
- Date of discharge.

At 12 months

- Usage of chemotherapy, radiotherapy, adjuvant therapy and entry into other trials.
- Tumour recurrences (date, site and method of diagnosis).

Annually

- Tumour recurrences (date, site and method of diagnosis).
- Status (date and cause of death if applicable).

Economic evaluation: additional information

The cost-effectiveness of the addition of MRI to triple assessment alone, from an NHS perspective, formed the primary economic evaluation end point.

Economic evaluation of health-care interventions involves combining measures of outcome with

Health resource use

Item of resource use	Source of resource use
Clinical assessment	
Neoadjuvant therapy	CRF
Mammography	CRF
USS	CRF
MR scan	CRF
FNA/core biopsy	CRF
Patient management	
Consumables	Clinical expert and CRF
Chemotherapy	CRF
Surgery	
Length of stay in hospital	CRF
Duration of main surgery	CRF
Time into anaesthetic room	CRF
Time into recovery room	CRF
Management of intraoperative complications	CRF
Duration of axillary surgery	CRF
Consumables	CRF
Drugs (anaesthetics, antibiotics, etc.)	CRF
Management of postoperative complications	CRF

Health resource use *(continued)*

Item of resource use	Source of resource use
Return to theatre	CRF
Blood transfusions	CRF
Fluid replacement	CRF
Histopathology tests	CRF
Post-operative complications after discharge	CRF
Repeated procedure, if relevant	
Length of stay in hospital	CRF
Duration of main surgery	CRF
Time into anaesthetic room	CRF
Time into recovery room	CRF
Management of intraoperative complications	CRF
Duration of axillary surgery	CRF
Consumables	CRF
Drugs (anaesthetics, antibiotics, etc.)	CRF
Management of postoperative complications	CRF
Return to theatre	CRF
Blood transfusions	CRF
Fluid replacement	CRF
Histopathology tests	CRF
Postoperative complications after discharge, if relevant	CRF
Follow-up visits	
Management of complications, if relevant	CRF
Length of stay of hospital readmission, if relevant	CRF
Duration of further surgery, if relevant	CRF
Theatre, anaesthetic and recovery room staff cost	CRF
Additional adjuvant therapy	CRF
Repeat MR scan	CRF
Other costs	
Extra costs (e.g. home help, childminding, etc.)	QoL questionnaire
Lost pay from work	QoL questionnaire
GP visits	QoL questionnaire
Outpatient hospital visits	CRF/QoL questionnaire
Day case visits	CRF
Time and composition of multidisciplinary team	Clinical Expert
Management of complications, if relevant	CRF
Consumables (surgery)	Clinical expert and CRF
Consumables (diagnostics)	Clinical expert and CRF
Histopathology tests	CRF
Cost of breast reconstruction	Clinical expert
Mammography	CRF
USS	CRF
MR scan	CRF
FNA/core biopsy	CRF

resource cost in an attempt to answer whether re-allocating resources from one programme to another represents a more efficient allocation of health-care resources. This was evaluated using cost-effectiveness analysis, where both the costs and consequences of a health-care intervention are compared with those of other relevant comparators.[66] In this study, conventional triple assessment alone was compared with triple assessment combined with MRI.

Quality-adjusted life-years are a generic measure of health outcome, which simultaneously capture both the morbidity (i.e. HRQoL gains) and the mortality (i.e. survival duration gains) of patients and combine the two into a single outcome measure. QALYs are calculated by splitting a patient's prognosis into discrete health states, which are characterised by different levels of HRQoL. QALYs are the summation across all health states of the length of time in a particular health state, multiplied by a weight representing the HRQoL for that health state. The HRQoL weights of the participants in the COMICE trial were measured using the EQ-5D questionnaire (a standardised instrument for measurement of health outcome).

The critical issue under consideration in COMICE is whether any additional (incremental) cost of the intervention is worth paying for its incremental benefits. If differences in outcome are demonstrated in COMICE, the decision rules developed to address this issue would focus on the incremental cost-effectiveness ratio (ICER), which is defined as:

$$ICER_{AB} = \frac{Costs_A - Costs_B}{QALYs_A - QALYs_B}$$

The decision about whether an intervention is considered cost-effective in this context hinges on the cost-effectiveness threshold considered appropriate by the health-care system. The value of the threshold is essentially an empirical question relating to the costs and benefits of the health-care programmes/interventions that will be displaced if a new, more expensive, intervention is funded by the system.[91] The threshold considered to be appropriate by the National Institute of Health and Clinical Effectiveness (NICE) is between £20,000 and £30,000.[92] Although NICE consider factors other than the cost-effectiveness of a new technology, if the ICER of the intervention is lower than this threshold then the intervention can be viewed as a cost-effective use of NHS resources, the extra benefits of the intervention outweigh the benefits of the intervention(s) that will be displaced to fund its extra cost. The decision rules of cost-effectiveness analysis can be extended to deal with multiple-treatment comparisons. Further discussions of such extensions and the related net benefit framework can be found in Drummond *et al.*[66]

Appendix 9

NSSI study patient information sheet

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 10

NSSI study patient consent form

(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 audiotape 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

Appendix 11

NSSI study proforma and response sheet

COMICE Well-Being Study

Section 1 Presurgical assessment

Q1 What investigations did you have before surgery?

Ultrasound	Yes	No
Fine needle aspiration	Yes	No
X-ray mammography	Yes	No
MRI	Yes	No

If not answered spontaneously prompt

Q2 How thoroughly was your cancer investigated before surgery?

Q2a
Record response and ask if she felt she was investigated:

Too thoroughly About right Too few investigations

Explore further and ask if she thought she had the right number of tests before surgery.

Q2b
Were the number of tests about right, too many or too few?

About right Too few Too many

Q3 Were any of the tests distressing (refer to list in Q1)

Ultrasound	Yes	No
Fine needle aspiration	Yes	No
X-ray mammography	Yes	No
MRI	Yes	No

If any of the tests were found to be distressing ask how distressing they were?

Ultrasound	– Not distressing	Slightly distressing	Moderately distressing	Very distressing
Fine needle aspiration	– Not distressing	Slightly distressing	Moderately distressing	Very distressing
X-ray mammography	– Not distressing	Slightly distressing	Moderately distressing	Very distressing
MRI	– Not distressing	Slightly distressing	Moderately distressing	Very distressing

Q3a
If any of the tests were distressing ask what was distressing and record the answer.

Section 2 Surgery

Q4 What type of surgery did you have?

Unilateral mastectomy
Bilateral mastectomy
Quadrant mastectomy
Wide local excision

If they had a mastectomy ask if they had any reconstruction. If yes ask if it was:

TRAM flap
LD
Implant

Q4a
When was the reconstruction carried out?

Immediately Delayed

Q5 How many nights did you spend in hospital (count the first night following surgery as night one)?

_____nights

Q6 Did you have any problems in hospital following your surgery? Yes ❑ No ❑

Q6a
If yes what problems did you have?

1.

2.

3.

4.

Q7 Looking back on your surgery were you given a choice about the type of surgery you had? Yes ❑ No ❑

Q7a
Was that helpful? Yes No

Q7b
On reflection do you think you made the right decision? Yes No

Q8 How satisfied are you with the shape of your breasts at present?

Very satisfied Satisfied Dissatisfied Very dissatisfied

If the patient had a second operation repeat Questions 5–8.

Q8a
How distressing did you find the second operation?

Not distressing Slightly distressing Moderately distressing Very distressing

Section 3 Adjuvant therapy

Q9 Have you had any treatment following surgery?

Radiotherapy	Yes	No	
Chemotherapy	Yes	No	
Hormone therapy	Yes	No	– tamoxifen
MAB	Yes	No	– trastuzumab (Herceptin; monoclonal antibodies)

Q9a
If RT how long after surgery did your treatment start? Record in weeks _____weeks

Was that: the right time too soon too late

Q9b
If CT how long after surgery did your treatment start? Record in weeks _____weeks

Was that: the right time too soon too late

Q9c
If HT how long after surgery did your treatment start? Record in weeks _____ weeks

Was that: the right time too soon too late

Q9d
If MAB how long after surgery did your treatment start? Record in weeks _____ weeks

Was that: the right time too soon too late

Q10 Are there any other treatments which you think might have benefited you

Record answers

Section 4 MRI

If patient had a scan (refer to Section 1) ask

Q11 How did you feel about the decision about having a scan?

Pleased Not pleased Indifferent

Q11a
On balance did it reassure you or make you anxious?

Reassured me Made me anxious

Why did it reassure you/make you anxious?

Section 5 Research knowledge

Q12 Before agreeing to take part in this study were you aware of any other breast cancer studies which were taking place?

Yes No

Q12a

If yes can you tell me what the studies were about? (record answer)

Q12b

Did it influence you in any way to take part in the study?

Yes No

Q12c

Where did you hear about these studies?

Newspaper Radio TV Magazine Friend/Relative

Section 6 In retrospect

Q13 What aspect of your treatment was done well? (record what patient says)

Q13a

What aspect of your treatment should have been done better? (record what patient says)

Q13b

If you could change one thing about your treatment what would it be? (record what patient says)

COMICE Well-Being Study

Patient name Patient ID Patient centre

Date of interview ___//___//___ Interview recorded Yes No

Section 1 Investigations

Q1

Ultrasound Yes ❑ No ❑

FNA Yes ❑ No ❑

X-ray Yes ❑ No ❑

MRI Yes ❑ No ❑

Q2 Thoroughness of investigations

What the patient said

Q2a

Record whether investigated

Too thoroughly ❑

About right ❑

Too few ❑

Q2b

Number of tests pre-surgery

About right ❑ Too many ❑ Too few ❑

Q3 Tests causing distress

Ultrasound	Yes ❑	No ❑	Not distressing	Slightly distressing	Moderately	Very distressing
FNA	Yes ❑	No ❑	Not distressing	Slightly distressing	Moderately	Very distressing
X-ray	Yes ❑	No ❑	Not distressing	Slightly distressing	Moderately	Very distressing
MRI	Yes ❑	No ❑	Not distressing	Slightly distressing	Moderately	Very distressing

Q3a
What was distressing (record what patient says)

Section 2 Surgery

Q4 Operation performed

Unilateral mastectomy	Yes ❑	No ❑	TRAM ❑	LD ❑	Implant ❑
Bilateral mastectomy	Yes ❑	No ❑	TRAM ❑	LD ❑	Implant ❑
Quadrant mastectomy	Yes ❑	No ❑			
Wide local excision	Yes ❑	No ❑			

Q4a
Reconstruction carried out Immediately ❑ Delayed ❑

Q5 Nights in hospital

____ nights (excluding preoperative nights)

Q6 Problems in hospital **Yes ❑** **No ❑**

Q6a
Problems encountered

1.

2.

3.

4.

Q7 Choice of surgery **Yes ❑** **No ❑**

Q7a
Helpful Yes ❑ No ❑

Q7b
Right decision Yes ❑ No ❑

Q7c
Reconstruction offered Yes ❑ No ❑

Q8 Satisfaction with shape of breast

Very satisfied ❑

Satisfied ❑

Dissatisfied ❑

Very dissatisfied ❑

Q8a
Second operation

Q8b
Nights in hospital _____nights (excluding preoperative nights)

Q8c
Problems in hospital Yes ❑ No ❑

Q8d
Problems encountered

1.

2.

3.

4.

Q8e
Choice of surgery Yes ❑ No ❑

Q8f
Helpful Yes ❑ No ❑

Q8g
Right decision Yes ❑ No ❑

Q8h
Reconstruction offered Yes ❑ No ❑

Q8i
Satisfaction with shape of breast

Very satisfied ❑

Satisfied ❑

Dissatisfied ❑

Very dissatisfied ❑

Q8j
Second operation level of distress

Not distressing ❑

Slightly distressing ❑

Moderately distressing ❑

Very distressing ❑

Section 3 Adjuvant therapy

Q9 Treatment following surgery

Radiotherapy Yes ❑ No ❑ (If yes go to Q10a)

Chemotherapy Yes ❑ No ❑ (If yes go to Q10b)

Hormone therapy Yes ❑ No ❑ (If yes go to Q10c)

MAB Yes ❑ No ❑ (If yes go to Q10d)

Q9a
Radiotherapy _____ weeks

Right time ❑ Too soon ❑ Too late ❑

Q9b
Chemotherapy _____ weeks

Right time ❑ Too soon ❑ Too late ❑

Q9c
Hormone therapy _____ weeks

Right time ❑ Too soon ❑ Too late ❑

Q9d
MAB _____ weeks

Right time ❑ Too soon ❑ Too late ❑

Q10 Other treatments that might have benefited (list)

1.

2.

3.

Section 4 MRI

Q11 Decision about having a scan

Pleased ❑ Not pleased ❑ Indifferent ❑

Q11a
Reassure or make anxious

Reassured me ❑ Made me anxious ❑

Response to Q11a

Section 5 Research knowledge

Q12 Aware of other breast cancer studies: Yes ❑ No ❑

Q12a
Knowledge of studies

Q12b
Influence to participate in study Yes ❑ No ❑

Q12c
Heard about studies from

Newspaper ❑ Radio ❑ TV ❑ Magazine ❑ Friend/Relative ❑

Section 6 In retrospect

Q13 Aspects of treatment which were done well
1.

Q13a
Aspects which could have been done better
1.

Q13b
What would you change?
1.

Appendix 12

A brief history of the COMICE trial

In 2000 the NIHR HTA programme published an open call for proposals to assess the cost-effectiveness of MRI within patients with breast cancer. The COMICE trial formally began in June 2001, and began recruiting in February 2002. It was planned that 1840 patients would be recruited over a 3-year period, and all patients would be followed up for 5 years. It was initially anticipated that eight centres would each recruit between six and eight patients per month, and the trial would complete in 2010.

In practice, recruitment rates were lower than anticipated. The entry of centres into the trial was slow, mainly due to regulatory delays, and recruitment was complicated by a lack of MR scanner time, shortages of radiologists and research nurses. Crucially, the patient pathway involved several hospital departments, and this complicated recruitment.

In June 2003, as a pragmatic solution to the problem of low patient recruitment, an active centre recruitment campaign was launched by the chief investigator's team. In total, 37 additional centres were recruited into the trial, and active steps were taken to sustain patient recruitment within those centres already in the trial. Monthly patient accrual rates steadily rose, and continued to rise until the end of the trial.

As a result of these efforts, in March 2005 the active recruitment phase of the trial was extended for 2 years. However, in order to achieve a timely final report, the follow-up period was abridged, allowing most patients to be followed up for 3 years (the period when most recurrences occur), instead of the 5 years initially intended. The trial completed recruitment in January 2007, with 1625 patients (ITT population 1623). Although this was below the initial target, it was sufficient for analytical purposes. Follow-up ceased in January 2008, and the final report was produced in October 2008. A summary of recruitment by year of randomisation is displayed below.

TABLE 38 *Recruitment by year of randomisation*

	MR scan, *n* (%)	No MR scan, *n* (%)	Total, *n* (%)
Total	816 (100.0)	807 (100.0)	1623 (100.0)
Year of randomisation			
2002	37 (4.5)	35 (4.3)	72 (4.4)
2003	102 (12.5)	102 (12.6)	204 (12.6)
2004	199 (24.4)	201 (24.9)	400 (24.6)
2005	221 (27.1)	210 (26.0)	431 (26.6)
2006	236 (28.9)	238 (29.5)	474 (29.2)
2007	21 (2.6)	21 (2.6)	42 (2.6)

Appendix 13

Additional summary tables

TABLE 39 *Mammography findings*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
Mammography details			
Number of lesions identified in the randomised breast			
0	54 (6.6)	49 (6.1)	103 (6.3)
1	707 (86.6)	715 (88.6)	1422 (87.6)
2	34 (4.2)	26 (3.2)	60 (3.7)
3	7 (0.9)	1 (0.1)	8 (0.5)
Missing	14 (1.7)	16 (2.0)	30 (1.8)
Number of lesions identified in the contralateral breast			
0	788 (96.6)	783 (97.0)	1571 (96.8)
1	12 (1.5)	8 (1.0)	20 (1.2)
2	2 (0.2)	0 (0.0)	2 (0.1)
Missing	14 (1.7)	16 (2.0)	30 (1.8)
Mass (n, %)			
Yes	626 (76.7)	603 (74.7)	1229 (75.7)
No	104 (12.7)	126 (15.6)	230 (14.2)
Unknown	1 (0.1)	1 (0.1)	2 (0.1)
Missing	85 (10.4)	77 (9.5)	162 (10.0)
Margin (n, %)			
C – spiculated	243 (29.8)	278 (34.4)	521 (32.1)
I – irregular	260 (31.9)	238 (29.5)	498 (30.7)
L – lobulated	42 (5.1)	22 (2.7)	64 (3.9)
S – smooth	35 (4.3)	41 (5.1)	76 (4.7)
U – uncertain	55 (6.7)	43 (5.3)	98 (6.0)
W –well-defined	19 (2.3)	7 (0.9)	26 (1.6)
Missing – N/A	162 (19.9)	178 (22.1)	340 (20.9)
Density (n, %)			
H – high	343 (42.0)	351 (43.5)	694 (42.8)
I – intermediate	302 (37.0)	274 (34.0)	576 (35.5)
L – low	7 (0.9)	6 (0.7)	13 (0.8)
Missing – N/A	164 (20.1)	176 (21.8)	340 (20.9)
Microcalcification (n, %)			
Yes	168 (20.6)	176 (21.8)	344 (21.2)
No	541 (66.3)	542 (67.2)	1083 (66.7)
Unknown	0 (0.0)	1 (0.1)	1 (0.1)
Missing	107 (13.1)	88 (10.9)	195 (12.0)

continued

TABLE 39 *Mammography findings (continued)*

	MR scan	No MR scan	Total
Microcalcification with mass (n, %)			
Yes	104 (12.7)	93 (11.5)	197 (12.1)
No	61 (7.5)	79 (9.8)	140 (8.6)
Missing – N/A	651 (79.8)	635 (78.7)	1286 (79.2)
Distribution (n, %)			
C – cluster	139 (17.0)	138 (17.1)	277 (17.1)
S – segmental	30 (3.7)	31 (3.8)	61 (3.8)
Missing	647 (79.3)	638 (79.1)	1285 (79.2)
Stromal deformity (n, %)			
Yes	149 (18.3)	167 (20.7)	316 (19.5)
No	535 (65.6)	540 (66.9)	1075 (66.2)
Unknown	5 (0.6)	1 (0.1)	6 (0.4)
Missing	127 (15.6)	99 (12.3)	226 (13.9)
Skin changes (n, %)			
Yes	15 (1.8)	22 (2.7)	37 (2.3)
No	673 (82.5)	693 (85.9)	1366 (84.2)
Missing	128 (15.7)	92 (11.4)	220 (13.6)
Asymmetric density (n, %)			
Yes	152 (18.6)	145 (18.0)	297 (18.3)
No	535 (65.6)	559 (69.3)	1094 (67.4)
Unknown	1 (0.1)	0 (0.0)	1 (0.1)
Missing	128 (15.7)	103 (12.8)	231 (14.2)
Site of mass (n, %)			
AX	13 (1.6)	16 (2.0)	29 (1.8)
C	23 (2.8)	25 (3.1)	48 (3.0)
IH	29 (3.6)	17 (2.1)	46 (2.8)
LH	38 (4.7)	27 (3.3)	65 (4.0)
LIQ	58 (7.1)	61 (7.6)	119 (7.3)
LOQ	34 (4.2)	48 (5.9)	82 (5.1)
OH	51 (6.3)	32 (4.0)	83 (5.1)
SAR	12 (1.5)	2 (0.2)	14 (0.9)
UH	61 (7.5)	57 (7.1)	118 (7.3)
UIQ	87 (10.7)	62 (7.7)	149 (9.2)
UOQ	271 (33.2)	307 (38.0)	578 (35.6)
Missing – N/A	139 (17.0)	153 (19.0)	292 (18.0)
Site of microcalcification (n, %)			
AX	5 (0.6)	2 (0.2)	7 (0.4)
C	7 (0.9)	7 (0.9)	14 (0.9)
IH	5 (0.6)	1 (0.1)	6 (0.4)
LH	7 (0.9)	6 (0.7)	13 (0.8)
LIQ	18 (2.2)	14 (1.7)	32 (2.0)
LOQ	8 (1.0)	9 (1.1)	17 (1.0)
OH	12 (1.5)	12 (1.5)	24 (1.5)

TABLE 39 *Mammography findings (continued)*

	MR scan	No MR scan	Total
SAR	4 (0.5)	1 (0.1)	5 (0.3)
UH	15 (1.8)	14 (1.7)	29 (1.8)
UIQ	18 (2.2)	20 (2.5)	38 (2.3)
UOQ	70 (8.6)	83 (10.3)	153 (9.4)
Missing – N/A	647 (79.3)	638 (79.1)	1285 (79.2)
Appearance of microcalcification – not mutually exclusive (n, %)			
Benign	16 (2.0)	18 (2.2)	34 (2.1)
Branching	10 (1.2)	11 (1.4)	21 (1.3)
Casting	18 (2.2)	25 (3.1)	43 (2.6)
Linear	27 (3.3)	25 (3.1)	52 (3.2)
Missing	654 (80.1)	637 (78.9)	1291 (79.5)
Other	3 (0.4)	3 (0.4)	6 (0.4)
Punctate	51 (6.3)	44 (5.5)	95 (5.9)
Variable	88 (10.8)	113 (14.0)	201 (12.4)
Size (mm)			
Mean (SD)	16.70 (8.37)	16.47 (7.85)	16.59 (8.11)
Median (range)	15.0 (4.0 to 80.0)	15.0 (1.0 to 50.0)	15.0 (1.0 to 80.0)
Missing	111	103	214
n	705	704	1409
Proximity to skin (mm)			
Mean (SD)	28.80 (16.93)	27.00 (15.36)	27.90 (16.19)
Median (range)	25.0 (0.0 to 110)	24.0 (0.0 to 110)	25.0 (0.0 to 110)
Missing	97	90	187
n	719	717	1436
Proximity to chest wall (mm)			
Mean (SD)	34.39 (24.71)	36.06 (25.07)	35.22 (24.89)
Median (range)	30.0 (0.0 to 140)	30.0 (0.0 to 130)	30.0 (0.0 to140)
Missing	107	111	218
n	709	696	1405
Proximity to nipple (mm)			
Mean (SD)	65.32 (28.67)	62.74 (27.31)	64.04 (28.02)
Median (range)	60.0 (0.0 to 165)	60.0 (0.0 to 200)	60.0 (0.0 to 200)
Missing	99	95	194
n	717	712	1429
Lesion score (n, %)			
Normal	1 (0.1)	0 (0.0)	1 (0.1)
Benign	12 (1.5)	7 (0.9)	19 (1.2)
Probably benign	95 (11.6)	88 (10.9)	183 (11.3)
Probably malignant	230 (28.2)	236 (29.2)	466 (28.7)
Malignant	375 (46.0)	384 (47.6)	759 (46.8)
Missing	103 (12.6)	92 (11.4)	195 (12.0)

continued

TABLE 39 *Mammography findings (continued)*

	MR scan	No MR scan	Total
Nodal involvement according to mammography (n, %)			
Yes	31 (3.8)	33 (4.1)	64 (3.9)
No	709 (86.9)	700 (86.7)	1409 (86.8)
Missing	76 (9.3)	74 (9.2)	150 (9.2)

AX, axillary tail; C, central; IH, inner half; LH, lateral half; LIQ, left inner quadrant; LOQ, left outer quadrant; OH, outer half; SAR, sub-areolar; UH, upper half; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

TABLE 40 *Ultrasound findings*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
USS details			
Number of lesions identified in the randomised breast (n, %)			
0	72 (8.8)	76 (9.4)	148 (9.1)
1	688 (84.3)	679 (84.1)	1367 (84.2)
2	30 (3.7)	22 (2.7)	52 (3.2)
3	5 (0.6)	3 (0.4)	8 (0.5)
Missing	21 (2.6)	27 (3.3)	48 (3.0)
Number of lesions identified in the contralateral breast (n, %)			
0	784 (96.1)	770 (95.4)	1554 (95.7)
1	10 (1.2)	10 (1.2)	20 (1.2)
2	1 (0.1)	0 (0.0)	1 (0.1)
Missing	21 (2.6)	27 (3.3)	48 (3.0)
Mass (n, %)			
Yes	714 (87.5)	689 (85.4)	1403 (86.4)
No	7 (0.9)	7 (0.9)	14 (0.9)
Unknown	1 (0.1)	1 (0.1)	2 (0.1)
Missing	94 (11.5)	110 (13.6)	204 (12.6)
Definition (n, %)			
I – irregular	362 (44.4)	366 (45.4)	728 (44.9)
P – poorly defined	288 (35.3)	275 (34.1)	563 (34.7)
W – well defined	65 (8.0)	54 (6.7)	119 (7.3)
Missing	101 (12.4)	112 (13.9)	213 (13.1)
Echo pattern (n, %)			
H – highly reflective	21 (2.6)	18 (2.2)	39 (2.4)
M – mixed	158 (19.4)	135 (16.7)	293 (18.1)
P – poorly reflective	519 (63.6)	526 (65.2)	1045 (64.4)
T – transonic	18 (2.2)	11 (1.4)	29 (1.8)
Missing	100 (12.3)	117 (14.5)	217 (13.4)
Distal effect (n, %)			
C – accentuation	57 (7.0)	57 (7.1)	114 (7.0)
N – none	255 (31.3)	258 (32.0)	513 (31.6)
T – attenuation	398 (48.8)	369 (45.7)	767 (47.3)
Missing	106 (13.0)	123 (15.2)	229 (14.1)

TABLE 40 *Ultrasound findings (continued)*

	MR scan	No MR scan	Total
Diffusal abnormality (n, %)			
Yes	44 (5.4)	45 (5.6)	89 (5.5)
No	658 (80.6)	631 (78.2)	1289 (79.4)
Unknown	4 (0.5)	6 (0.7)	10 (0.6)
Missing	110 (13.5)	125 (15.5)	235 (14.5)
Site of mass (n, %)			
AX	9 (1.1)	17 (2.1)	26 (1.6)
C	12 (1.5)	16 (2.0)	28 (1.7)
IH	16 (2.0)	17 (2.1)	33 (2.0)
LH	29 (3.6)	24 (3.0)	53 (3.3)
LIQ	54 (6.6)	61 (7.6)	115 (7.1)
LOQ	58 (7.1)	57 (7.1)	115 (7.1)
OH	41 (5.0)	37 (4.6)	78 (4.8)
SAR	7 (0.9)	2 (0.2)	9 (0.6)
UH	69 (8.5)	55 (6.8)	124 (7.6)
UIQ	121 (14.8)	79 (9.8)	200 (12.3)
UOQ	295 (36.2)	328 (40.6)	623 (38.4)
Missing	105 (12.9)	114 (14.1)	219 (13.5)
Size (mm)			
Mean (SD)	14.62 (7.17)	14.57 (8.36)	14.59 (7.77)
Median (range)	14.0 (2.0, 72.0)	13.0 (1.0, 93.0)	13.0 (1.0, 93.0)
Missing	99	109	208
n	717	698	1415
Proximity to skin (mm)			
Mean (SD)	11.40 (6.91)	11.26 (6.89)	11.33 (6.90)
Median (range)	10.0 (0.0, 60.0)	10.0 (0.0, 65.0)	10.0 (0.0, 65.0)
Missing	149	158	307
n	667	649	1316
Proximity to chest wall (mm)			
Mean (SD)	11.97 (10.67)	12.16 (10.49)	12.06 (10.58)
Median (range)	10.0 (0.0, 84.0)	10.0 (0.0, 90.0)	10.0 (0.0, 90.0)
Missing	204	205	409
n	612	602	1214
Proximity to nipple (mm)			
Mean (SD)	50.99 (25.30)	52.14 (30.26)	51.54 (27.75)
Median (range)	50.0 (1.0, 150)	50.0 (0.0, 400)	50.0 (0.0, 400)
Missing	455	481	936
n	361	326	687
Lesion score (n, %)			
Benign	6 (0.7)	6 (0.7)	12 (0.7)
Probably benign	40 (4.9)	33 (4.1)	73 (4.5)
Probably malignant	142 (17.4)	145 (18.0)	287 (17.7)
Malignant	503 (61.6)	485 (60.1)	988 (60.9)
Missing	125 (15.3)	138 (17.1)	263 (16.2)

continued

TABLE 40 *Ultrasound findings (continued)*

	MR scan	No MR scan	Total
Nodal involvement according to USS (n, %)			
Yes	53 (6.5)	60 (7.4)	113 (7.0)
No	616 (75.5)	578 (71.6)	1194 (73.6)
Missing	147 (18.0)	169 (20.9)	316 (19.5)

AX, axillary tail; C, central; IH, inner half; LH, lateral half; LIQ, left inner quadrant; LOQ, left outer quadrant; OH, outer half; SAR, sub-areolar; UH, upper half; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

TABLE 41 *MRI findings (ITT population)*

	MR scan
Total (*n*, %)	816 (100.0)
Had a scan? (n, %)	
Yes	761 (93.3)
No	53 (6.5)
Missing	2 (0.2)
Time from randomisation to MRI (days)	
Mean (SD)	4.24 (3.59)
Median (range)	3 (–4 to 21)
Missing	79
n	737
Pulse sequences successfully completed (n, %)	
Yes	716 (87.7)
No	19 (2.3)
Missing	81 (9.9)
Number of lesions identified in the randomised breast (n, %)	
0	28 (3.4)
1	585 (71.7)
2	94 (11.5)
3	29 (3.6)
4	5 (0.6)
5	2 (0.2)
Missing	73 (8.9)
Number of lesions identified in the contralateral breast (n, %)	
0	680 (83.3)
1	58 (7.1)
2	5 (0.6)
Missing	73 (8.9)

TABLE 41 *MRI findings (ITT population) (continued)*

	MR scan
***Margin* (n, %)**	
Smooth	78 (9.6)
Scalloped	30 (3.7)
Irregular	406 (49.8)
Spiculated	183 (22.4)
Missing	119 (14.6)
***Shape* (n, %)**	
Round	99 (12.1)
Oval	100 (12.3)
Lobulated	75 (9.2)
Irregular	359 (44.0)
Branching	15 (1.8)
Stellate	57 (7.0)
Missing	111 (13.6)
***Enhancement with lesion* (n, %)**	
Homogenous	221 (27.1)
Heterogeneous	349 (42.8)
Rim	117 (14.3)
Internal septations	6 (0.7)
None	6 (0.7)
Missing	117 (14.3)
***Overall lesion score* (n, %)**	
0	6 (0.7)
1	25 (3.1)
≥2	673 (82.5)
Missing	112 (13.7)
Size (mm)	
Mean (SD)	19.05 (9.95)
Median (range)	18.0 (0.8 to 99.0)
Missing	103
n	713
***Site of mass* (n, %)**	
AX	11 (1.3)
C	31 (3.8)
IH	18 (2.2)
LH	36 (4.4)
LIQ	45 (5.5)

continued

TABLE 41 *MRI findings (ITT population) (continued)*

	MR scan
LOQ	83 (10.2)
OH	82 (10.0)
SAR	14 (1.7)
UH	66 (8.1)
UIQ	110 (13.5)
UOQ	212 (26.0)
Missing	108 (13.2)
Proximity to skin (mm)	
Mean (SD)	22.30 (11.74)
Median (range)	20.0 (0.0 to 100.0)
Missing	111
n	705
Proximity to chest wall (mm)	
Mean (SD)	33.79 (22.40)
Median (range)	30.0 (0.0 to 130.0)
Missing	117
n	699
Proximity to nipple (mm)	
Mean (SD)	54.32 (22.64)
Median (range)	54.0 (0.0 to 145.0)
Missing	119
n	697
Additional biopsy performed (n, %)	
Yes	12 (1.5)
No	683 (83.7)
Missing	121 (14.8)
Type of biopsy (n, %)	
FNA	1 (8.3)
USS-guided FNA	2 (16.7)
Core biopsy	1 (8.3)
USS-guided core biopsy	7 (58.3)
Missing	1 (8.3)
Result of biopsy (n, %)	
Positive	9 (75.0)
Negative	3 (25.0)

AX, axillary tail; C, central; IH, inner half; LH, lateral half; LIQ, left inner quadrant; LOQ, left outer quadrant; OH, outer half; SAR, sub-areolar; UH, upper half; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

TABLE 42 *Surgery characteristics*

	MR scan	No MR scan	Total
Total (*n*, %)	816 (100.0)	807 (100.0)	1623 (100.0)
***Planned management in randomised breast* (n, %)**			
WLE	728 (89.2)	783 (97.0)	1511 (93.1)
Simple mastectomy	41 (5.0)	6 (0.7)	47 (2.9)
Simple mastectomy + LDMF ± prosthesis	2 (0.2)	0 (0.0)	2 (0.1)
Simple mastectomy + TRAM	2 (0.2)	0 (0.0)	2 (0.1)
Simple mastectomy + expander	1 (0.1)	1 (0.1)	2 (0.1)
Skin-sparing mastectomy + LDMF ± prosthesis	7 (0.9)	0 (0.0)	7 (0.4)
Skin-sparing mastectomy + TRAM	0 (0.0)	1 (0.1)	1 (0.1)
Skin-sparing mastectomy and expander	2 (0.2)	0 (0.0)	2 (0.1)
Quadrantectomy	7 (0.9)	2 (0.2)	9 (0.6)
Quadrantectomy and miniflap	1 (0.1)	0 (0.0)	1 (0.1)
Primary chemotherapy	1 (0.1)	0 (0.0)	1 (0.1)
Other	2 (0.2)	1 (0.1)	3 (0.2)
Missing	22 (2.7)	13 (1.6)	35 (2.2)
***Initial surgery* (n, %)**			
WLE	750 (91.9)	787 (97.5)	1537 (94.7)
Mastectomy	58 (7.1)	10 (1.2)	68 (4.2)
Quadrantectomy and miniflap	1 (0.1)	0 (0.0)	1 (0.1)
Other	2 (0.2)	0 (0.0)	2 (0.1)
Did not have surgery	2 (0.2)	2 (0.2)	4 (0.2)
Lost to follow-up	1 (0.1)	1 (0.1)	2 (0.1)
Missing	2 (0.2)	7 (0.9)	9 (0.6)
Time from randomisation to surgery (days)			
Mean (SD)	15.80 (14.40)	14.51 (10.11)	15.16 (12.46)
Median (range)	14.0 (-1.0, 243)	13.0 (1.0, 142)	13.0 (–1.0 to 243)
Missing	7	6	13
n	809	801	1610
***Axillary surgery performed* (n, %)**			
Yes	758 (92.9)	744 (92.2)	1502 (92.5)
No	49 (6.0)	56 (6.9)	105 (6.5)
Missing	9 (1.1)	7 (0.9)	16 (1.0)
***Type of axillary surgery* (n, %)**			
Clearance	290 (38.3)	283 (38.0)	573 (38.1)
Clearance and sentinel node biopsy	33 (4.4)	24 (3.2)	57 (3.8)
Sample	257 (33.9)	257 (34.5)	514 (34.2)
Sample and sentinel node biopsy	76 (10.0)	75 (10.1)	151 (10.1)
Sentinel node biopsy	99 (13.1)	103 (13.8)	202 (13.4)
Missing	3 (0.4)	2 (0.3)	5 (0.3)

continued

TABLE 42 *Surgery characteristics (continued)*

	MR scan	No MR scan	Total
Clear margin obtained (n, %)			
Yes	773 (94.7)	761 (94.3)	1534 (94.5)
No	10 (1.2)	21 (2.6)	31 (1.9)
Missing	33 (4.0)	25 (3.1)	58 (3.6)
Type of ward admitted to (n, %)			
General surgical ward	804 (98.5)	796 (98.6)	1600 (98.6)
High-dependency ward	1 (0.1)	0 (0.0)	1 (0.1)
None	0 (0.0)	1 (0.1)	1 (0.1)
Missing	11 (1.3)	10 (1.2)	21 (1.3)

LDMF, latissimus dorsi muscle flap; TRAM, traverse rectus abdominus myocutaneous.

TABLE 43 *Pathology: predictive markers*

	MR scan, *n* (%)	No MR scan, *n* (%)	Total, *n* (%)
Total	816 (100.0)	807 (100.0)	1623 (100.0)
Predictive markers			
ER status			
Positive	620 (76.0)	622 (77.1)	1242 (76.5)
Negative	113 (13.8)	112 (13.9)	225 (13.9)
Unknown	52 (6.4)	40 (5.0)	92 (5.7)
Missing	31 (3.8)	33 (4.1)	64 (3.9)
PR status			
Positive	409 (50.1)	414 (51.3)	823 (50.7)
Negative	164 (20.1)	167 (20.7)	331 (20.4)
Unknown	210 (25.7)	188 (23.3)	398 (24.5)
Missing	33 (4.0)	38 (4.7)	71 (4.4)
HER2 status known			
Known	324 (39.7)	341 (42.3)	665 (41.0)
Unknown	419 (51.3)	400 (49.6)	819 (50.5)
Missing	73 (8.9)	66 (8.2)	139 (8.6)
HER2 status			
0	225 (69.4)	219 (64.2)	444 (66.8)
1	49 (15.1)	56 (16.4)	105 (15.8)
2	23 (7.1)	25 (7.3)	48 (7.2)
3	27 (8.3)	41 (12.0)	68 (10.2)

Appendix 14

Per-protocol population summary tables

TABLE 44 *Baseline characteristics (per-protocol population)*

	MR scan	No MR scan	Total
Total (*n*, %)	751 (100.0)	827 (100.0)	1578 (100.0)
Randomised allocation			
MR scan	744 (99.1)	49 (5.9)	793 (50.3)
No MR scan	7 (0.9)	778 (94.1)	785 (49.7)
Minimisation factors			
Number of patients recruited by randomised surgeon (n, %)			
< 10	105 (14.0)	120 (14.5)	225 (14.3)
≥ 10	646 (86.0)	707 (85.5)	1353 (85.7)
Age (as randomised) (n, %)			
< 50 years	170 (22.6)	195 (23.6)	365 (23.1)
≥ 50 years	581 (77.4)	632 (76.4)	1213 (76.9)
Breast density (n, %)			
ACR BI-RADS group 1	92 (12.3)	108 (13.1)	200 (12.7)
ACR BI-RADS group 2	659 (87.7)	719 (86.9)	1378 (87.3)
Year of randomisation (n, %)			
2002	37 (4.9)	34 (4.1)	71 (4.5)
2003	96 (12.8)	105 (12.7)	201 (12.7)
2004	183 (24.4)	209 (25.3)	392 (24.8)
2005	199 (26.5)	211 (25.5)	410 (26.0)
2006	215 (28.6)	247 (29.9)	462 (29.3)
2007	21 (2.8)	21 (2.5)	42 (2.7)
Initial clinical details			
Age at randomisation (n, %)			
Mean (SD)	56.35 (9.67)	56.57 (10.14)	56.46 (9.92)
Median (range)	57 (27 to 86)	57 (28 to 85)	57 (27 to 86)
n	751	827	1578
Employment (n, %)			
Working full-time	240 (32.0)	266 (32.2)	506 (32.1)
Working part-time	181 (24.1)	182 (22.0)	363 (23.0)
Unable to work due to illness/disability	24 (3.2)	16 (1.9)	40 (2.5)
Retired	234 (31.2)	281 (34.0)	515 (32.6)
At home, not looking for work	54 (7.2)	63 (7.6)	117 (7.4)
Unemployed, looking for work	8 (1.1)	8 (1.0)	16 (1.0)
Student	6 (0.8)	4 (0.5)	10 (0.6)
Missing	4 (0.5)	7 (0.8)	11 (0.7)

continued

TABLE 44 *Baseline characteristics (per-protocol population) (continued)*

	MR scan	No MR scan	Total
Hospital			
< 10	50 (6.7)	62 (7.5)	112 (7.1)
10–20	78 (10.4)	87 (10.5)	165 (10.5)
≥ 20	623 (83.0)	678 (82.0)	1301 (82.4)
Menopausal status			
Premenopausal	212 (28.2)	244 (29.5)	456 (28.9)
Postmenopausal	532 (70.8)	573 (69.3)	1105 (70.0)
Missing data	7 (0.9)	10 (1.2)	17 (1.1)
Contraceptive pill/slow release injection use:			
Currently	22 (2.9)	29 (3.5)	51 (3.2)
Previously	426 (56.7)	488 (59.0)	914 (57.9)
Never	297 (39.5)	302 (36.5)	599 (38.0)
Missing	6 (0.8)	8 (1.0)	14 (0.9)
How long taken for (years) – currently taking pill			
Mean (SD)	12.73 (8.76)	14.71 (8.55)	13.84 (8.61)
Median (range)	13.5 (1.0 to 30.0)	14.5 (1.0 to 32.0)	14.0 (1.0 to 32.0)
Missing	0	1	1
n	22	28	50
How long taken for (years) – previously taken pill			
Mean (SD)	8.02 (6.18)	7.55 (6.24)	7.77 (6.21)
Median (range)	6.0 (1.0 to 30.0)	5.0 (0.0 to 35.0)	6.0 (0.0 to 35.0)
Missing	20	21	41
sn	406	467	873
HRT use:			
Currently	60 (8.0)	47 (5.7)	107 (6.8)
Previously	216 (28.8)	235 (28.4)	451 (28.6)
Never	470 (62.6)	542 (65.5)	1012 (64.1)
Missing	5 (0.7)	3 (0.4)	8 (0.5)
How long taken for (years) – currently taking HRT			
Mean (SD)	10.16 (5.90)	8.79 (6.82)	9.57 (6.31)
Median (range)	8.5 (0.0 to 23.0)	7.0 (1.0 to 32.0)	8.0 (0.0 to 32.0)
Missing	2	4	6
n	58	43	101
How long taken for (years) – previously taken HRT			
Mean (SD)	8.04 (5.78)	7.40 (5.29)	7.71 (5.53)
Median (range)	7.0 (0.0 to 27.0)	6.5 (1.0 to 30.0)	7.0 (0.0 to 30.0)
Missing	6	11	17
n	210	224	434
Cancer identified through screening			
Yes	384 (51.1)	442 (53.4)	826 (52.3)
No	365 (48.6)	381 (46.1)	746 (47.3)
Missing data	2 (0.3)	4 (0.5)	6 (0.4)

TABLE 44 *Baseline characteristics (per-protocol population) (continued)*

	MR scan	No MR scan	Total
Method of confirming primary breast cancer			
FNA	63 (8.4)	79 (9.6)	142 (9.0)
Core biopsy	587 (78.2)	638 (77.1)	1225 (77.6)
Both	97 (12.9)	102 (12.3)	199 (12.6)
Missing	4 (0.5)	8 (1.0)	12 (0.8)
Time from confirmatory histological sample to randomisation (days)			
Mean (SD)	13.93 (7.89)	14.03 (8.58)	13.98 (8.25)
Median (range)	13.0 (0.0 to 49.0)	13.5 (–24 to 94.0)	13.0 (–24 to 94.0)
Missing	6	9	15
n	745	818	1563
Preoperative neoadjuvant therapy (n, %)			
Yes	6 (0.8)	10 (1.2)	16 (1.0)
No	744 (99.1)	813 (98.3)	1557 (98.7)
Missing data	1 (0.1)	4 (0.5)	5 (0.3)
Type of therapy (n, %)			
Tamoxifen	4 (66.7)	6 (60.0)	10 (62.5)
Anastrozole	2 (33.3)	1 (10.0)	3 (18.8)
Other	0 (0.0)	3 (30.0)	3 (18.8)

TABLE 45 *MRI findings (preprotocol population)*

	MR scan
Total (*n*, %)	751 (100.0)
Time from randomisation to MRI (days)	
Mean (SD)	4.31 (3.72)
Median (range)	3 (0, 28)
Missing	17
n	734
Pulse sequences successfully completed (n, %)	
Yes	712 (94.8)
No	19 (2.5)
Miss	20 (2.7)
Number of lesions identified in the randomised breast (n, %)	
0	29 (3.9)
1	586 (78.0)
2	92 (12.3)
3	27 (3.6)
4	4 (0.5)
5	2 (0.3)
Missing	11 (1.5)

continued

TABLE 45 *MRI findings (preprotocol population) (continued)*

	MR scan
***Number of lesions identified in the contralateral breast* (n, %)**	
0	679 (90.4)
1	56 (7.5)
2	5 (0.7)
Missing	11 (1.5)
***Margin* (n, %)**	
Smooth	79 (10.5)
Scalloped	30 (4.0)
Irregular	403 (53.7)
Spiculated	181 (24.1)
Missing	58 (7.7)
***Shape* (n, %)**	
Round	99 (13.2)
Oval	100 (13.3)
Lobulated	76 (10.1)
Irregular	354 (47.1)
Branching	15 (2.0)
Stellate	57 (7.6)
Missing	50 (6.7)
***Enhancement with lesion* (n, %)**	
Homogenous	222 (29.6)
Heterogeneous	343 (45.7)
Rim	119 (15.8)
Internal septations	6 (0.8)
None	5 (0.7)
Missing	56 (7.5)
***Overall lesion score* (n, %)**	
0	6 (0.8)
1	26 (3.5)
≥2	668 (88.9)
Missing	51 (6.8)
***Size (mm)* (n, %)**	
Mean (SD)	19.05 (9.96)
Median (range)	18.0 (0.8 to 99.0)
Missing	42
n	709
***Site of mass* (n, %)**	
AX	11 (1.5)
C	31 (4.1)
IH	19 (2.5)
LH	34 (4.5)

TABLE 45 *MRI findings (preprotocol population) (continued)*

	MR scan
LIQ	44 (5.9)
LOQ	84 (11.2)
OH	84 (11.2)
SAR	14 (1.9)
UH	64 (8.5)
UIQ	107 (14.2)
UOQ	212 (28.2)
Missing	47 (6.3)
Proximity to skin (mm)	
Mean (SD)	22.28 (11.74)
Median (range)	20.0 (0.0 to 100.0)
Missing	51
n	700
Proximity to chest wall (mm)	
Mean (SD)	33.87 (22.32)
Median (range)	30.0 (0.0 to 130.0)
Missing	57
n	694
Proximity to nipple (mm)	
Mean (SD)	54.34 (22.57)
Median (range)	54.0 (0.0 to 145.0)
Missing	59
n	692
Additional biopsy performed	
Yes	11 (1.5)
No	680 (90.5)
Miss	60 (8.0)
Type of biopsy (n, %)	
FNA	1 (9.1)
USS-guided FNA	2 (18.2)
Core biopsy	1 (9.1)
USS-guided core biopsy	6 (54.5)
Missing	1 (9.1)
Result of biopsy (n, %)	
Positive	8 (72.7)
Negative	3 (27.3)

AX, axillary tail; C, central; IH, inner half; LH, lateral half; LIQ, left inner quadrant; LOQ, left outer quadrant; OH, outer half; SAR, sub-areolar; UH, upper half; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

Appendix 15

Additional clinical results tables

TABLE 46 *Efficiency of imaging: agreement in size of the index lesion for patients with invasive carcinoma alone*

MRI							Mammography		
T-stage MRI (frequency, %)	T-stage pathology						T-stage mammography (frequency, %)	T-stage pathology	
	T1a	T1b	T1c	T2	T3			T1a	T1b
T1a	2	5	2	0	0	9	T1a	14	16
	(11.76)	(4.35)	(0.72)	(0.00	(0.00			(40.00)	(7.48)
T1b	10	51	35	3	0	99	T1b	11	118
	(58.82)	(44.35)	(12.64)	(2.19)	(0.00)			(31.43)	(55.14)
T1c	5	49	165	31	0	250	T1c	7	71
	(29.41	42.61)	59.57)	22.63)	0.00)			(20.00)	(33.18)
T2	0	9	73	100	4	186	T2	3	8
	(0.00)	(7.83)	(26.35)	(72.99)	(80.00)			(8.57)	(3.74)
T3	0	1	2	3	1	7	T3	0	1
	(0.00)	(0.87)	(0.72)	(2.19)	(20.00)			(0.00)	(0.47)
Total	17	115	277	137	5	551	Total	35	214
Weighted kappa (95% CI)	0.4470 (0.3908 to 0.5031)						0.4493 (0.4050 to 0.4936)		

TABLE 47 *Efficiency of imaging: agreement in size of the index lesion for patients with invasive carcinoma + DCIS*

MRI							Mammography		
T-stage MRI (frequency, %)	T-stage pathology						T-stage mammography (frequency, %)	T-stage pathology	
	T1a	T1b	T1c	T2	T3			T1a	T1b
T1a	0	6	2	0	0	8	T1a	6	17
	(0.00	(6.98)	(0.81)	(0.00)	(0.00)			(40.00)	(10.83)
T1b	3	43	40	4	0	90	T1b	6	93
	(60.00)	(50.00)	(16.19)	(2.42)	(0.00)			(40.00)	(59.24)
T1c	2	33	153	43	2	233	T1c	3	45
	(40.00)	(38.37)	(61.94)	(26.06)	(16.67)			(20.00)	(28.66)
T2	0	3	51	114	9	177	T2	0	2
	(0.00)	(3.49)	(20.65)	(69.09)	(75.00)			(0.00)	(1.27)
T3	0	1	1	4	1	7	T3	0	0
	(0.00)	(1.16)	(0.40)	(2.42)	(8.33)			(0.00)	(0.00)
Total	5	86	247	165	12	515	Total	15	157
Weighted kappa (95% CI)	0.4767 (0.4198 to 0.5336)						0.4114 (0.3675 to 0.4553)		

				USS						
					T-stage pathology					
T1c	**T2**	**T3**		**T-stage USS (frequency, %)**	**T1a**	**T1b**	**T1c**	**T2**	**T3**	
8	2	1	41	T1a	15	32	19	2	0	68
(1.49)	(0.78)	(25.00)			(50.00)	(14.48)	(3.37)	(0.73)	(0.00)	
90	17	0 0.00	236	T1b	12	135	134	11	0 0.00	292
(16.79)	(6.61				(40.00)	(61.09)	(23.76)	(4.00)		
353	92	1	524	T1c	2	46	362	130	2	542
(65.86)	(35.80)	(25.00)			(6.67)	(20.81)	(64.18)	(47.27)	(33.33)	
85	145	2	243	T2	1	4	48	132	4	189
(15.86)	(56.42)	(50.00)			(3.33)	(1.81)	(8.51)	(48.00)	(66.67)	
0	1	0	2	T3	0	4	1	0	0	5
(0.00)	(0.39)	(0.00)			(0.00)	(1.81)	(0.18)	(0.00)	(0.00)	
536	257	4	1046	Total	30	221	564	275	6	1096
				0.4551 (0.4148 to 0.4955)						

				USS						
					T-stage pathology					
T1c	**T2**	**T3**		**T-stage USS (frequency, %)**	**T1a**	**T1b**	**T1c**	**T2**	**T3**	
8	4	1	36	T1a	7	31	21	6	0	65
(1.62)	(1.25)	(7.14)			(46.67)	(18.67)	(4.10)	(1.79)	(0.00)	
100	25	2	226	T1b	7	101	144	24	2	278
(20.20)	(7.84)	(14.29)			(46.67)	(60.84)	(28.13)	(7.14)	(13.33)	
320	131	6	505	T1c	1	31	308	168	7	515
(64.65)	(41.07)	(42.86)			(6.67)	(18.67)	(60.16)	(50.00)	(46.67)	
66	158	5	231	T2	0	0	37	138	6	181
(13.33)	(49.53)	(35.71)			(0.00)	(0.00)	(7.23)	(41.07)	(40.00)	
1	1	0	2	T3	0	3	2	0	0	5
(0.20)	(0.31)	(0.00)			(0.00)	(1.81)	(0.39)	(0.00)	(0.00)	
495	319	14	1000	Total	15	166	512	336	15	1044
				0.3803 (0.3407 to 0.4200)						

TABLE 48 *Chemotherapy: time from surgery to starting chemotherapy*

	MR scan (*n* = 321)	No MR scan (*n* = 300)	Total (*n* = 621)
Time from initial surgery to receiving chemotherapy (months)			
Mean (SD)	1.6 (0.84)	1.6 (0.86)	1.6 (0.85)
Median (range)	1.4 (0.2 to 6.0)	1.4 (0.2 to 5.9)	1.4 (0.2 to 6.0)
Missing	78	71	149

TABLE 49 *Chemotherapy: type of chemotherapy received within 6 months of initial surgery*

	MR scan (*n* = 321)	No MR scan (*n* = 300)	Total (*n* = 621)
	n (%)	*n* (%)	*n* (%)
5FU (± adriamycin and cyclophosphamide)	13 (4.0)	9 (3.0)	22 (3.5)
Adriamycin (± cyclophosphamide)	8 (2.5)	2 (0.7)	10 (1.6)
Capecitabine	5 (1.6)	0 (0.0)	5 (0.8)
Cyclophosphamide (± methotrexate, 5FU)	57 (17.8)	47 (15.7)	104 (16.7)
Taxane (docetaxel/paclitaxel ± gemcitabine), *or* taxol + gemcitabine and carboplatin, *or* ± FEC	24 (7.5)	26 (8.7)	50 (8.1)
Doxorubicin (± cyclophosphamide)	2 (0.6)	1 (0.3)	3 (0.5)
Epirubicin [± capecitabine or CMF or cyclophosphamide or taxane (± gemcitabine)], or given as FEC	223 (69.5)	214 (71.3)	437 (70.4)
Gemcitabine	2 (0.6)	2 (0.7)	4 (0.6)
Methotrexate	0 (0.0)	1 (0.3)	1 (0.2)
Missing data/unknown	78 (24.3)	69 (23.0)	147 (23.7)

5FU, fluorouracil; CMF, cyclophosphamide, methotrexate and fluorouracil; FEC, fluorouracil, epirubicin and cyclophosphamide.

TABLE 50 *Radiotherapy: time from initial surgery to receiving radiotherapy (within 6 months)*

	MR scan (*n* = 553)	No MR scan (*n* = 553)	Total (*n* = 1106)
Time from initial surgery to receiving radiotherapy (months)			
Mean (SD)	3.1 (1.38)	3.1 (1.33)	3.1 (1.36)
Median (range)	2.9 (0.9 to 6.0)	2.7 (0.7 to 6.0)	2.8 (0.7 to 6.0)
Missing	83	83	166

TABLE 51 *Radiotherapy: site of radiotherapy (within 6 months)*

	MR scan (*n* = 553)	No MR scan (*n* = 553)	Total (*n* = 1106)
	n (%)	*n* (%)	*n* (%)
Breast	435 (78.7)	437 (79.0)	872 (78.8)
Breast and boost (including breast scar and tumour bed boost and tumour boost)	108 (19.5)	114 (20.6)	222 (20.1)
Breast and SCF (and breast boost and SCF)	6 (1.1)	10 (1.8)	16 (1.4)
Axilla	2 (0.4)	3 (0.5)	5 (0.5)
Chest wall	12 (2.2)	9 (1.6)	21 (1.9)
SCF	2 (0.4)	6 (1.1)	8 (0.7)
Breast and chest wall (± SCF)	3 (0.5)	2 (0.4)	5 (0.5)
Breast, axilla (± breast, axilla and SCF and breast and lymph)	5 (0.9)	9 (1.6)	14 (1.3)
Chest wall and axilla	0 (0.0)	1 (0.2)	1 (0.1)
Other	5 (0.9)	11 (2.0)	16 (1.4)
Chest wall and SCF (including chest wall/axilla/SCF)	4 (0.7)	2 (0.4)	6 (0.5)
Missing data	79 (14.3)	77 (13.9)	156 (14.1)

SCF, supraclavicular fossa.

TABLE 52 *Additional adjuvant therapies: time from initial surgery to receiving adjuvant therapy (within 6 months of initial surgery)*

	MR scan (*n* = 511)	No MR scan (*n* = 494)	Total (*n* = 1005)
Time from initial surgery to receiving additional adjuvant therapy (months)			
Mean (SD)	1.6 (1.64)	1.6 (1.69)	1.6 (1.66)
Median (range)	0.9 (0.0 to 6.0)	0.9 (0.0 to 6.0)	0.9 (0.0 to 6.0)
Missing	95	78	173

TABLE 53 *Additional adjuvant therapies: type of adjuvant therapy received within 6 months of initial surgery*

	MR scan (*n* = 511), *n* (%)	No MR scan (*n* = 494), *n* (%)	Total (*n* = 1005), *n* (%)
Anastrozole	109 (21.3)	106 (21.5)	215 (21.4)
Exemestane	5 (1.0)	8 (1.6)	13 (1.3)
Trastuzumab	0 (0.0)	3 (0.6)	3 (0.3)
Trial (ibandronate/placebo)	0 (0.0)	1 (0.2)	1 (0.1)
Trial (tamoxifen/anastrozole)	0 (0.0)	1 (0.2)	1 (0.1)
Letrozole	16 (3.1)	22 (4.5)	38 (3.8)
Megestrol	2 (0.4)	2 (0.4)	4 (0.4)
Tamoxifen	341 (66.7)	316 (64.0)	657 (65.4)
Toremifine	1 (0.2)	0 (0.0)	1 (0.1)
Zoladex	4 (0.8)	7 (1.4)	11 (1.1)
Zoledronic acid	2 (0.4)	3 (0.6)	5 (0.5)
Other	3 (0.6)	1 (0.2)	4 (0.4)
Missing	72 (14.1)	60 (12.1)	132 (13.1)

TABLE 54 *Clinical significance of < 5-mm MRI-only-detected lesions: repeat MRI findings*

	Total (*n* = 14)
Time from randomisation to repeat MRI (days)	
Mean (SD)	439.0 (93.20)
Median (range)	453.0 (247.0 to 574.0)
N/A or missing	0
Time from start of radiotherapy to receiving repeat MRI (days)	
Mean (SD)	341.1 (108.74)
Median (range)	392.0 (111.0 to 504.0)
N/A or missing	2
Were pulse sequences successfully completed? (n, %)	
Yes	13 (92.9)
No	1 (7.1)
Number of lesions identified in the randomised breast (n, %)	
0	13 (92.9)
1	1 (7.1)
Number of lesions identified in the contralateral breast (n, %)	
0	13 (92.9)
1	1 (7.1)
Margin (n, %)	
Smooth	1 (7.1)
Scalloped	1 (7.1)
N/A or missing	12 (85.7)

TABLE 54 *Clinical significance of < 5-mm MRI-only-detected lesions: repeat MRI findings (continued)*

	Total (*n* = 14)
***Shape* (n, %)**	
Oval	1 (7.1)
Lobulated	1 (7.1)
N/A or missing	12 (85.7)
***Enhancement with lesion* (n, %)**	
Homogeneous	2 (14.3)
Missing	12 (85.7)
***Overall lesion score* (n, %)**	
1	2 (14.3)
N/A or missing	12 (85.7)
***Size (mm)* (n, %)**	
Mean (SD)	4.5 (0.71)
Median (range)	4.5 (4.0 to 5.0)
N/A or missing	12
***Site of mass* (n, %)**	
UH	1 (7.1)
UOQ	1 (7.1)
N/A or missing	12 (85.7)
Proximity to skin (mm)	
Mean (SD)	38.5 (16.26)
Median (Range)	38.5 (27.0 to 50.0)
N/A or Missing	12
Proximity to chest (mm)	
Mean (SD)	43.0 (9.90)
Median (range)	43.0 (36.0 to 50.0)
N/A or missing	12
Proximity to nipple RAC (mm)	
Mean (SD)	55.5 (7.78)
Median (range)	55.5 (50.0 to 61.0)
N/A or missing	12
***Additional biopsy performed?* (n, %)**	
No	2 (14.3)
N/A or missing	12 (85.7)

UH, upper half; UOQ, upper outer quadrant.

TABLE 55 *Clinical significance of ≥ 5-mm biopsy-negative MRI-only-detected lesions: repeat MRI findings*

	Clinically significant	
	Yes (*n* = 3)	**No (*n* = 18)**
Time from randomisation to repeat MRI (days)		
Mean (SD)	573.7 (258.43)	464.3 (114.41)
Median (range)	463.0 (389.0 to 869.0)	437.0 (250.0 to 764.0)
N/A or missing	0	0
Time from start of radiotherapy to receiving repeat MRI (days)		
Mean (SD)	662.0 [0]	340.1 (128.08)
Median (range)	662.0 (662.0 to 662.0)	364.5 (142.0 to 530.0)
N/A or missing	2	4
Were pulse sequences successfully completed? (n, %)		
Yes	3 (100.0)	18 (100.0)
Number of lesions identified in the randomised breast (n, %)		
0	2 (66.7)	16 (88.9)
1	1 (33.3)	1 (5.6)
2	0 (0.0)	1 (5.6)
Number of lesions identified in the contralateral breast (n, %)		
0	0 (0.0)	12 (66.7)
1	3 (100.0)	6 (33.3)
Margin (n, %)		
Smooth	2 (66.7)	3 (16.7)
Scalloped	1 (33.3)	0 (0.0)
Irregular	0 (0.0)	2 (11.1)
N/A or missing	0 (0.0)	13 (72.2)
Shape (n, %)		
Round	0 (0.0)	1 (5.6)
Oval	2 (66.7)	2 (11.1)
Lobulated	1 (33.3)	0 (0.0)
Irregular	0 (0.0)	2 (11.1)
N/A or missing	0 (0.0)	13 (72.2)
Enhancement with lesion (n, %)		
Homogenous	3 (100.0)	4 (22.2)
Heterogeneous	0 (0.0)	1 (5.6)
N/A or missing	0 (0.0)	13 (72.2)
Overall lesion score (n, %)		
1	0 (0.0)	3 (16.7)
2	3 (100.0)	0 (0.0)
3	0 (0.0)	2 (11.1)
N/A or missing	0 (0.0)	13 (72.2)

TABLE 55 *Clinical significance of ≥ 5-mm biopsy-negative MRI-only-detected lesions: repeat MRI findings (continued)*

	Clinically significant	
	Yes (*n* = 3)	**No (*n* = 18)**
Size (mm)		
Mean (SD)	10.0 (2.65)	11.8 (13.03)
Median (range)	9.0 (8.0 to 13.0)	6.0 (5.0 to 35.0)
N/A or missing	0	13
Site of mass (n, %)		
LIQ	1 (33.3)	0 (0.0)
LOQ	1 (33.3)	1 (5.6)
OH	0 (0.0)	1 (5.6)
UH	1 (33.3)	0 (0.0)
UOQ	0 (0.0)	3 (16.7)
N/A or missing	0 (0.0)	13 (72.2)
Proximity to skin (mm)		
Mean (SD)	12.0 (5.29)	15.6 (12.58)
Median (range)	10.0 (8.0 to 18.0)	10.0 (5.0 to 37.0)
N/A or missing	0	13
Proximity to chest (mm)		
Mean (SD)	35.0 (12.49)	59.8 (35.47)
Median (range)	39.0 (21.0 to 45.0)	76.0 (3.0 to 90.0)
N/A or missing	0	13
Proximity to nipple RAC (mm)		
Mean (SD)	37.0 (25.16)	38.6 (24.15)
Median (range)	24.0 (21.0 to 66.0)	36.0 (10.0 to 77.0)
N/A or missing	0	13
Additional biopsy performed? (n, %)		
Yes	1 (33.3)	2 (11.1)
No	2 (66.7)	3 (16.7)
N/A or missing	0 (0.0)	13 (72.2)
Type of biopsy (n, %)		
MRC	0 (0.0)	1 (5.6)
N/A or missing	3 (100.0)	17 (94.4)
Result (n, %)		
Negative	0 (0.0)	2 (11.1)
N/A or missing	3 (100.0)	16 (88.9)

LIQ, lower inner quadrant, LOQ; lower outer quadrant; MRC, MR-controlled; OH, outer half; RAC, retro-areolar complex; UH, upper half, UOQ, upper outer quadrant.

Appendix 16

Baseline characteristics of the QoL population

TABLE 56 *Quality of life: baseline characteristics of the QoL population*

	MR scan	No MR scan	Total
Total (*n*, %)	727 (100.0)	719 (100.0)	1446 (100.0)
Minimisation factors			
Number of patients recruited by randomised surgeon (n, %)			
< 10	92 (12.7)	96 (13.4)	188 (13.0)
≥ 10	635 (87.3)	623 (86.6)	1258 (87.0)
Age (as randomised) (n, %)			
< 50 years	161 (22.1)	160 (22.3)	321 (22.2)
≥ 50 years	566 (77.9)	559 (77.7)	1125 (77.8)
Breast density (n, %)			
BI-RADS group 1 (1)	86 (11.8)	89 (12.4)	175 (12.1)
BI-RADS group 2 (2, 3, 4)	641 (88.2)	630 (87.6)	1271 (87.9)
Year of randomisation (n, %)			
2002	36 (5.0)	34 (4.7)	70 (4.8)
2003	99 (13.6)	98 (13.6)	197 (13.6)
2004	177 (24.3)	184 (25.6)	361 (25.0)
2005	198 (27.2)	186 (25.9)	384 (26.6)
2006	198 (27.2)	198 (27.5)	396 (27.4)
2007	19 (2.6)	19 (2.6)	38 (2.6)
Initial clinical details			
Age at randomisation (n, %)			
Mean (SD)	56.40 (9.57)	56.61 (9.86)	56.51 (9.71)
Median (range)	57 (27 to 86)	57 (29 to 85)	57 (27 to 86)
n	727	719	1446
Employment (n, %)			
Working full-time	227 (31.2)	229 (31.8)	456 (31.5)
Working part-time	183 (25.2)	164 (22.8)	347 (24.0)
Unable to work due to illness/disability	16 (2.2)	15 (2.1)	31 (2.1)
Retired	229 (31.5)	240 (33.4)	469 (32.4)
At home, not looking for work	52 (7.2)	57 (7.9)	109 (7.5)
Unemployed, looking for work	10 (1.4)	6 (0.8)	16 (1.1)
Student	6 (0.8)	2 (0.3)	8 (0.6)
Missing	4 (0.6)	6 (0.8)	10 (0.7)

continued

TABLE 56 *Quality of life: baseline characteristics of the QoL population (continued)*

	MR scan	No MR scan	Total
Hospital (n, %)			
< 10	41 (5.6)	48 (6.7)	89 (6.2)
10–20	73 (10.0)	69 (9.6)	142 (9.8)
≥20	613 (84.3)	602 (83.7)	1215 (84.0)
Menopausal status (n, %)			
Premenopausal	206 (28.3)	202 (28.1)	408 (28.2)
Postmenopausal	515 (70.8)	509 (70.8)	1024 (70.8)
Missing data	6 (0.8)	8 (1.1)	14 (1.0)
Cancer identified through screening (n, %)			
Yes	374 (51.4)	394 (54.8)	768 (53.1)
No	349 (48.0)	322 (44.8)	671 (46.4)
Missing data	4 (0.6)	3 (0.4)	7 (0.5)
Method of confirming primary breast cancer (n, %)			
FNA	57 (7.8)	69 (9.6)	126 (8.7)
Core biopsy	562 (77.3)	559 (77.7)	1121 (77.5)
Both	103 (14.2)	85 (11.8)	188 (13.0)
Missing	5 (0.7)	6 (0.8)	11 (0.8)
Time from confirmatory histological sample to randomisation (days)			
Mean (SD)	14.08 (7.80)	14.38 (9.01)	14.23 (8.42)
Median (range)	13 (0 to 49)	14 (–24 to 94)	14 (–24 to 94)
Missing	6	9	15
n	721	710	1431
Preoperative neoadjuvant therapy (n, %)			
Yes	5 (0.7)	11 (1.5)	16 (1.1)
No	720 (99.0)	704 (97.9)	1424 (98.5)
Missing data	2 (0.3)	4 (0.6)	6 (0.4)
Type of therapy (n, %)			
Tamoxifen	3 (60.0)	6 (54.5)	9 (56.3)
Arimidex	2 (40.0)	1 (9.1)	3 (18.8)
Other	0 (0.0)	4 (36.4)	4 (25.0)

TABLE 56 *Quality of life: baseline characteristics of the QoL population (continued)*

	MR scan	No MR scan	Total
Contraceptive pill/slow release injection use (n, %)			
Currently	20 (2.8)	24 (3.3)	44 (3.0)
Previously	429 (59.0)	443 (61.6)	872 (60.3)
Never	272 (37.4)	246 (34.2)	518 (35.8)
Missing	6 (0.8)	6 (0.8)	12 (0.8)
How long taken for (years) – currently taking pill			
Mean (SD)	12.95 (8.64)	14.74 (8.67)	13.91 (8.60)
Median (range)	13.5 (1.0 to 30.0)	15.0 (1.0 to 32.0)	14.0 (1.0 to 32.0)
Missing	0	1	1
n	20	23	43
How long taken for (years) – previously taken pill			
Mean (SD)	8.10 (6.20)	7.51 (6.15)	7.80 (6.18)
Median (range)	6.0 (1.0 to 30.0)	5.0 (0.0 to 35.0)	6.0 (0.0 to 35.0)
Missing	16	19	35
n	413	424	837
HRT use (n, %)			
Currently	57 (7.8)	44 (6.1)	101 (7.0)
Previously	210 (28.9)	216 (30.0)	426 (29.5)
Never	456 (62.7)	457 (63.6)	913 (63.1)
Missing	4 (0.6)	2 (0.3)	6 (0.4)
How long taken for (years) – currently taking HRT			
Mean (SD)	9.75 (5.71)	8.43 (6.14)	9.19 (5.90)
Median (range)	8.0 (0.0 to 23.0)	6.5 (1.0 to 32.0)	8.0 (0.0 to 32.0)
Missing	2	4	6
n	55	40	95
How long taken for (years) – previously taken HRT			
Mean (SD)	7.98 (5.73)	7.37 (5.31)	7.68 (5.53)
Median (range)	6.5 (0.0 to 27.0)	6.0 (1.0 to 30.0)	6.0 (0.0 to 30.0)
Missing	4	11	15
n	206	205	411

Appendix 17

Additional economic evaluation results

TABLE 57 *Summary of key resource use from initial surgery*

	Observations	Mean	SD
Time in anaesthetic room (min)			
MRI arm	594	15.98317	15.75614
No MRI	601	14.81531	13.37052
Time in theatre (min)			
MRI arm	585	65.55726	40.86753
No MRI	599	59.93823	28.15374
Time in recovery room (min)			
MRI arm	702	65.29772	50.85353
No MRI	702	63.02707	46.30154
Time for axillary surgery (min)			
MRI arm	433	27.71593	15.29267
No MRI	434	27.29032	14.7751
Time spent in hospital for initial operation (nights)			
MRI arm	808	3.54703	13.72162
No MRI	800	2.86375	3.281562
Did patient experience postoperative complications?			
	Yes (*n*, %)	**No (*n*, %)**	
MRI arm	76 (9.38%)	734 (90.62%)	
No MRI	84 (10.47%)	718 (89.53%)	
Was the patient returned to theatre?			
	Yes (*n*, %)	**No (*n*, %)**	
MRI arm	12 (16.00%)	63 (84.00%)	
No MRI	11 (13.10%)	73 (86.90%)	
Did the patient receive fluid replacement?			
	Yes (*n*, %)	**No (*n*, %)**	
MRI arm	40 (53.33%)	35 (46.67%)	
No MRI	41 (48.81%)	43 (51.19%)	
Was the patient placed in a high-dependency ward?			
	Yes (*n*, %)	**No (*n*, %)**	
MRI arm	1 (1.33%)	74 (98.67%)	
No MRI	0 (0.00%)	84 (100.00%)	

TABLE 58 *Summary of resource use from follow-up to 12 months post initial surgery*

	Yes (*n*, %)	No (*n*, %)
First post-operative follow-up		
Did the patient experience complications after leaving hospital?		
MRI arm	219 (26.94)	594 (73.06)
No MRI	201 (25.16)	598 (74.84)
Was the patient admitted to hospital as a result of the complication?		
MRI arm	6 (2.75)	212 (97.25)
No MRI	13 (6.47)	188 (93.53)
Repeat operation		
Was a repeat operation carried out?		
MRI arm	141 (17.36)	671 (82.64)
No MRI	162 (20.15)	642 (79.85)
6-month follow-up		
Did the patient experience complications after leaving hospital?		
MRI arm	189 (25.93)	540 (74.07)
No MRI	197 (27.10)	530 (72.90)
Was the patient readmitted to hospital?		
MRI arm	40 (21.28)	148 (78.72)
No MRI	37 (18.78)	160 (81.22)
Has the patient undergone an oophorectomy?		
MRI arm	3 (0.59)	507 (99.41)
No MRI	5 (1.01)	492 (98.99)
Has the patient undergone further surgery?		
MRI arm	10 (1.97)	498 (98.03)
No MRI	9 (1.80)	490 (98.20)
12-month follow-up		
Has the patient being readmitted to hospital?		
MRI arm	86 (11.64)	653 (88.36)
No MRI	74 (10.10)	659 (89.90)
Has the patient received chemotherapy?		
MRI arm	257 (34.73)	483 (65.27)
No MRI	242 (32.75)	497 (67.25)
Has the patient received radiotherapy?		
MRI arm	627 (84.73)	113 (15.27)
No MRI	641 (86.74)	98 (13.26)
Has the patient undergone oophorectomy?		
MRI arm	43 (5.83)	695 (94.17)
No MRI	39 (5.36)	689 (94.64)
Has the patient received further surgery?		
MRI arm	34 (4.59)	707 (95.41)
No MRI	31 (4.21)	706 (95.79)

TABLE 59 *Prices and unit costs of major resource items*

Resource	Cost	Unit	Source
Initial surgery			
Theatre cost	£4.47	Per minute	PSSRU and expert opinion
Anaesthetic room cost	£1.77	Per minute	PSSRU and expert opinion
Recovery room cost	£0.68	Per minute	PSSRU and expert opinion
Axillary surgery cost	£4.47	Per minute	PSSRU and expert opinion
Cost per night in hospital	£231	Per night	NHS reference costs
Repeat surgery			
WLE	£1567	Total costs	NHS reference costs
Simple mastectomy	£2400	Total costs	NHS reference costs
Simple mastectomy + LDMF	£2400	Total costs	NHS reference costs
Simple mastectomy + LDMF with prosthesis	£2400	Total costs	NHS reference costs
Simple mastectomy + TRAM	£2400	Total costs	NHS reference costs
Simple mastectomy + expander	£2400	Total costs	NHS reference costs
Skin-sparing mastectomy	£2400	Total costs	NHS reference costs
Skin-sparing mastectomy + LDMF	£2400	Total costs	NHS reference costs
Skin-sparing mastectomy + LDMF with prosthesis	£2400	Total costs	NHS reference costs
Skin-sparing mastectomy + TRAM	£2400	Total costs	NHS reference costs
Skin-sparing mastectomy + expander	£2400	Total costs	NHS reference costs
Quadrantectomy	£1567	Total costs	NHS reference costs
Quadrantectomy and miniflap	£1567	Total costs	NHS reference costs
Oophorectomy	£2785	Total costs	NHS reference costs
Chemotherapy			
Procure chemotherapy drugs for regimens in Band 1	£70	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 2	£424	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 3	£660	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 4	£590	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 5	£434	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 6	£918	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 7	£1400	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 8	£1706	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 9	£840	Per cycle	NHS reference costs
Procure chemotherapy drugs for regimens in Band 10	£1129	Per cycle	NHS reference costs

continued

TABLE 59 *Prices and unit costs of major resource items (continued)*

Resource	Cost	Unit	Source
Deliver exclusively oral chemotherapy	£221		NHS reference costs
Deliver simple parenteral chemotherapy at *first* attendance	£213		NHS reference costs
Deliver more complex parenteral chemotherapy at first attendance	£177		NHS reference costs
Deliver complex chemotherapy	£302		NHS reference costs
Deliver subsequent elements of a chemotherapy cycle	£212		NHS reference costs
Radiotherapy			
Delivery of a fraction of radiotherapy	£106	Total costs	NHS reference costs
GP visits			
GP visit	£34	Per visit	PSSRU

LDMF, latissimus dorsi muscle flap; PSSRU, Personal Social Services Research Unit; TRAM, traverse rectus abdominus myocutaneous.

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al*.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al*.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.*

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al.*, on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al.*

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al.*

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al.*

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, *et al.*

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, *et al.*

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, *et al.*

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.
By Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, *et al.*

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.
By Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, *et al.*

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.
By McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, *et al.*

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, *et al.*

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

No. 27
Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.
By Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al.*

No. 28
A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).
By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al.*

No. 29
Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.
By Andronis L, Barton P, Bryan S.

Suppl. 1
Trastuzumab for the treatment of primary breast cancer in HER2-positive women: a single technology appraisal.
By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.
By Chilcott J, Lloyd Jones M, Wilkinson A.

The use of paclitaxel in the management of early stage breast cancer.
By Griffin S, Dunn G, Palmer S, Macfarlane K, Brent S, Dyker A, *et al.*

Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma.
By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.
By Green C, Bryant J, Takeda A, Cooper K, Clegg A, Smith A, *et al.*

Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.
By Walker S, Palmer S, Erhorn S, Brent S, Dyker A, Ferrie L, *et al.*

Erlotinib for the treatment of relapsed non-small cell lung cancer.
By McLeod C, Bagust A, Boland A, Hockenhull J, Dundar Y, Proudlove C, *et al.*

Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.
By Griffin S, Walker S, Sculpher M, White S, Erhorn S, Brent S, *et al.*

Infliximab for the treatment of adults with psoriasis.
By Loveman E, Turner D, Hartwell D, Cooper K, Clegg A.

No. 30
Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.
By Morrell CJ, Warner R, Slade P, Dixon S, Walters S, Paley G, *et al*.

No. 31
The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.
By Rogowski R, Burch J, Palmer S, Craigs C, Golder S, Woolacott N.

No. 32
Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.
By Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, *et al*.

No. 33
A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.
By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al*., on behalf of the 3CPO study investigators.

No. 34
Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.
By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

No. 35
Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.
By Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al*.

No. 36
Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.
By Hewitt CE, Gilbody SM, Brealey S, Paulden M, Palmer S, Mann R, *et al*.

No. 37
A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.
By Williamson I, Benge S, Barton S, Petrou S, Letley L, Fasey N, *et al*.

No. 38
The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model.
By Bond M, Pitt M, Akoh J, Moxham T, Hoyle M, Anderson R.

No. 39
Rehabilitation of older patients: day hospital compared with rehabilitation at home. A randomised controlled trial.
By Parker SG, Oliver P, Pennington M, Bond J, Jagger C, Enderby PM, *et al*.

No. 40
Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis
By Renfrew MJ, Craig D, Dyson L, McCormick F, Rice S, King SE, *et al*.

No. 41
The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation.
By Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, *et al.*

No. 42
Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness.
By Daniels J, Gray J, Pattison H, Roberts T, Edwards E, Milner P, *et al.*

No. 43
Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Honest H, Forbes CA, Durée KH, Norman G, Duffy SB, Tsourapas A, *et al*.

No. 44
The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model.
By Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS, *et al*.

Suppl. 2
Gemcitabine for the treatment of metastatic breast cancer.
By Jones J, Takeda A, Tan SC, Cooper K, Loveman E, Clegg A.

Varenicline in the management of smoking cessation: a single technology appraisal.
By Hind D, Tappenden P, Peters J, Kenjegalieva K.

Alteplase for the treatment of acute ischaemic stroke: a single technology appraisal.
By Lloyd Jones M, Holmes M.

Rituximab for the treatment of rheumatoid arthritis.
By Bagust A, Boland A, Hockenhull J, Fleeman N, Greenhalgh J, Dundar Y, *et al*.

Omalizumab for the treatment of severe persistent allergic asthma.
By Jones J, Shepherd J, Hartwell D, Harris P, Cooper K, Takeda A, *et al*.

Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma.
By Boland A, Bagust A, Hockenhull J, Davis H, Chu P, Dickson R.

Adalimumab for the treatment of psoriasis.
By Turner D, Picot J, Cooper K, Loveman E.

Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal.
By Holmes M, C Carroll C, Papaioannou D.

Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal.
By Mowatt G, Boachie C, Crowther M, Fraser C, Hernández R, Jia X, *et al*.

Sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer.
By Bond M, Hoyle M, Moxham T, Napier M, Anderson R.

No. 45
Vitamin K to prevent fractures in older women: systematic review and economic evaluation.
By Stevenson M, Lloyd-Jones M, Papaioannou D.

No. 46
The effects of biofeedback for the treatment of essential hypertension: a systematic review.
By Greenhalgh J, Dickson R, Dundar Y.

No. 47
A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study.
By Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, *et al*.

Suppl. 3
Lapatinib for the treatment of HER2-overexpressing breast cancer.
By Jones J, Takeda A, Picot J, von Keyserlingk C, Clegg A.

Infliximab for the treatment of ulcerative colitis.
By Hyde C, Bryan S, Juarez-Garcia A, Andronis L, Fry-Smith A.

Rimonabant for the treatment of overweight and obese people.
By Burch J, McKenna C, Palmer S, Norman G, Glanville J, Sculpher M, *et al*.

Telbivudine for the treatment of chronic hepatitis B infection.
By Hartwell D, Jones J, Harris P, Cooper K.

Entecavir for the treatment of chronic hepatitis B infection.
By Shepherd J, Gospodarevskaya E, Frampton G, Cooper, K.

Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal.
By Stevenson M, Pandor A.

Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal.
By Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E.

Cetuximab for the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck.
By Greenhalgh J, Bagust A, Boland A, Fleeman N, McLeod C, Dundar Y, *et al*.

Mifamurtide for the treatment of osteosarcoma: a single technology appraisal.
By Pandor A, Fitzgerald P, Stevenson M, Papaioannou D.

Ustekinumab for the treatment of moderate to severe psoriasis.
By Gospodarevskaya E, Picot J, Cooper K, Loveman E, Takeda A.

No. 48
Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model.
By Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, *et al*.

No. 49
Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation.
By Chen Y-F, Jowett S, Barton P, Malottki K, Hyde C, Gibbs JSR, *et al*.

No. 50
Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY) – a pharmacoepidemiological and qualitative study.
By Wong ICK, Asherson P, Bilbow A, Clifford S, Coghill D, R DeSoysa R, *et al*.

No. 51
ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening.
By Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, *et al*.

No. 52
The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation.
By Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, *et al*.

No. 53
Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks' gestation (TOPS).
By Robson SC, Kelly T, Howel D, Deverill M, Hewison J, Lie MLS, *et al*.

No. 54
Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.
By Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S, *et al*.

No. 55
VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers.
By Dumville JC, Worthy G, Soares MO, Bland JM, Cullum N, Dowson C, *et al*.

No. 56
A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial
By Michaels JA, Campbell WB, King BM, MacIntyre J, Palfreyman SJ, Shackley P, *et al*.

No. 57
Communication of carrier status information following universal newborn screening for sickle cell disorders and cystic fibrosis: qualitative study of experience and practice.
By Kai J, Ulph F, Cullinan T, Qureshi N.

No. 58
Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation.
By Burch J, Paulden M, Conti S, Stock C, Corbett M, Welton NJ, *et al*.

No. 59
Development of a toolkit and glossary to aid in the adaptation of health technology assessment (HTA) reports for use in different contexts.
By Chase D, Rosten C, Turner S, Hicks N, Milne R.

No. 60
Colour vision testing for diabetic retinopathy: a systematic review of diagnostic accuracy and economic evaluation.
By Rodgers M, Hodges R, Hawkins J, Hollingworth W, Duffy S, McKibbin M, *et al*.

No. 61
Systematic review of the effectiveness and cost-effectiveness of weight management schemes for the under fives: a short report.
By Bond M, Wyatt K, Lloyd J, Welch K, Taylor R.

No. 62
Are adverse effects incorporated in economic models? An initial review of current practice.
By Craig D, McDaid C, Fonseca T, Stock C, Duffy S, Woolacott N.

Health Technology Assessment programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Observers

Diagnostic Technologies & Screening Panel

Members

Chair,
Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Deputy Chair,
Dr David Elliman,
Consultant Paediatrician and Honorary Senior Lecturer, Great Ormond Street Hospital, London

Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, Imaging Science and Biomedical Engineering, Cancer & Imaging Sciences, University of Manchester

Ms Jane Bates, Consultant Ultrasound Practitioner, Ultrasound Department, Leeds Teaching Hospital NHS Trust

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, Director of Programmes, UK National Screening Committee

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, Service User Representative

Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds

Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

Observers

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody, Programme Manager, Neuroscience and Mental Health Board

Dr Ursula Wells, Principal Research Officer, Department of Health

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Deputy Chair,
Professor Imti Choonara,
Professor in Child Health, University of Nottingham

Mrs Nicola Carey, Senior Research Fellow, School of Health and Social Care, The University of Reading

Mr John Chapman, Service User Representative

Dr Peter Elton, Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Mrs Barbara Greggains, Service User Representative

Dr Bill Gutteridge, Medical Adviser, London Strategic Health Authority

Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University

Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, Consultant Psychiatrist and Head of Department, University of Birmingham

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

Dr Martin Shelly, General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester

Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Mr David Symes, Service User Representative

Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

Observers

Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health

Mr Simon Reeve, Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

Dr Heike Weber, Programme Manager, Medical Research Council

Dr Ursula Wells, Principal Research Officer, Department of Health

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)

Therapeutic Procedures Panel

Members

Chair,
Dr John C Pounsford,
Consultant Physician, North Bristol NHS Trust

Deputy Chair,
Professor Scott Weich,
Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry

Professor Jane Barlow,
Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry

Ms Maree Barnett,
Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill,
Service User Representative

Mrs Anthea De Barton-Watson,
Service User Representative

Mr Mark Emberton,
Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London

Professor Steve Goodacre,
Professor of Emergency Medicine, University of Sheffield

Professor Christopher Griffiths,
Professor of Primary Care, Barts and The London School of Medicine and Dentistry

Mr Paul Hilton,
Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Nicholas James,
Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital

Dr Peter Martin,
Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Dr Kate Radford,
Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston

Mr Jim Reece
Service User Representative

Dr Karen Roberts,
Nurse Consultant, Dunston Hill Hospital Cottages

Observers

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Department of Health

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), London

Deputy Chair,
Dr David Pencheon,
Director, NHS Sustainable Development Unit, Cambridge

Dr Elizabeth Fellow-Smith,
Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson,
General Practitioner, Parkway Medical Centre, Newcastle upon Tyne

Professor Mike Kelly,
Director, Centre for Public Health Excellence, NICE, London

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset

Ms Jeanett Martin,
Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton,
Locum Consultant in Public Health Medicine, Bristol Primary Care Trust

Miss Nicky Mullany,
Service User Representative

Professor Ian Roberts,
Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Professor Ken Stein,
Senior Clinical Lecturer in Public Health, University of Exeter

Dr Kieran Sweeney,
Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth

Professor Carol Tannahill,
Glasgow Centre for Population Health

Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

Observers

Ms Christine McGuire,
Research & Development, Department of Health

Dr Caroline Stone,
Programme Manager, Medical Research Council

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Professor of Social Gerontology & Health Services Research, University of Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer and Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing and Head of Research, The Medical School, University of Birmingham

Professor Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, Institute of Child Health, London

Mr John Dunning, Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Dean of Faculty of Medicine, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts and The London School of Medicine and Dentistry

Mr Leonard R Fenwick, Chief Executive, Freeman Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher, Antenatal Teacher and Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, University of Birmingham

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Professor Fiona Gilbert, Consultant Radiologist and NCRN Member, University of Aberdeen

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, South Tees Hospital NHS Trust

Bec Hanley, Co-director, TwoCan Associates, West Sussex

Dr Maryann L Hardy, Senior Lecturer, University of Bradford

Mrs Sharon Hart, Healthcare Management Consultant, Reading

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham

Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London

Professor Allen Hutchinson, Director of Public Health and Deputy Dean of ScHARR, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278