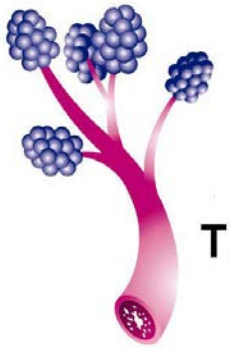

LORIS

The LOw RISk DCIS Trial

A Phase III Trial of Surgery versus Active Monitoring for Low Risk Ductal Carcinoma in Situ (DCIS)

Sponsor: University of Birmingham

Funded by NIHR Health Technology Assessment Programme

Protocol Version: 4.0, 15th March 2016

www.birmingham.ac.uk/loris

ISRCTN: 27544579	**HTA No.:** 11/36/16
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UNIVERSITY OF BIRMINGHAM

NHS National Institute for Health Research

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SIGNATURE PAGE

LORIS Trial Protocol Version 4.0, 15th March 2016

This protocol has been approved by:

Name: Miss Adele Francis **Trial Role:** Chief Investigator

Signature: _____ **Date:** 15/MAR/2016

This protocol describes the LORIS Trial and provides information about procedures for patients taking part in the LORIS Trial. The protocol should not be used as a guide for treatment of patients not taking part in this study.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
3	15-Mar-2016	4.0	Substantial amendment	• Eligibility criteria updated • Inclusion of all patients with locally diagnosed low or intermediate grade DCIS but deemed to have low risk disease on Central Histopathology Review • Clarification of acceptable methods for DCIS diagnosis • Clarification that all diagnostic biopsy slides must be submitted for Central Histopathology Review • Schedule of Events amended to reflect that VACB results must be available prior to patient registration • Clarification of the role of the Patient Information Leaflet • Update from recent trial data which compared anastrozole and tamoxifen • Insertion of radiology flowchart • Addition of 3 Case Report Forms
2	03-Jul-2015	3.0	Substantial amendment	• Aims, objectives and outcome measures further defined • Update to Background and Rationale section • Updated CRF Completion Guidance • Other minor amendments and corrections
1	12-Nov-2014	2.0	Substantial amendment	• Eligibility criteria extended to include patients diagnosed on open diagnostic surgical biopsy • Exclusion criteria amended to exclude patients with current invasive breast disease • Clarification that all diagnostic slides will be reviewed by the Central Histopathology Review Team prior to randomisation • Method of communicating mammogram outcome result no longer specified • Requirement to inform patients of mammogram outcome result within 2 weeks removed • Acceptable method of mammography image transfer expanded • Updated CRF completion Guidance • Updates to Flowchart 1 (Patient Pathway to Randomisation) and Flowchart 2 (Investigation Algorithm) • Other minor amendments and corrections

CONTACT DETAILS

Chief Investigator & Clinical Coordinator
Miss Adele Francis
Department of Surgery, Queen Elizabeth Hospital, Queen, Elizabeth Medical Centre, Birmingham , B15 2TH, UK
☎ +44 (0) 121 627 2000

Deputy Chief Investigator
Dr Daniel Rea
Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK
☎ +44 (0) 121 371 5124

Pathology Lead
Dr Jeremy Thomas
Pathology Directorate, Western General Hospital, Edinburgh, EH4 2XU, UK
☎ +44 (0) 131 537 1961

Quality of Life Lead
Prof Lesley Fallowfield
Sussex Health Outcomes, Research & Education in Cancer (SHORE-C), Brighton and Sussex Medical School, University of Sussex, Brighton, BN1 9RX, UK
☎ +00 (0) 1273 873 019

Radiology Lead
Dr Matthew Wallis
Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK
☎ +44 (0) 1223 586 578

Translational Lead
Prof John Bartlett
Ontario Institute for Cancer Research, Toronto, Ontario, Canada, M5G 0A3
☎ +00 (1) 647 259 4241

Statistical Lead
Lucinda Billingham
CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK
☎ +44 (0) 121 414 3790

Health Economics Lead
Prof Tracy Roberts
Health Economics Unit, University of Birmingham, Birmingham, B15 2TT, UK
☎ +00 (0) 121 414 7708

Trial Statistician
Ms Sarah Pirrie
CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK
☎ +44 (0) 121 414 9065

Senior Trial Manager
Dr Sarah Bowden
CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK
☎ +44 (0) 121 414 4371

Trial Management Team Leader
Miss Claire Gaunt
CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK
☎ +44 (0) 121 414 3057

Trial Coordinator
Miss Jennie Young
CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT
☎ +44 (0) 121 414 3017

Other Co-Investigators

Prof David Dodwell, St. James's Hospital, Leeds, UK
Prof Andrew Evans, University of Dundee, UK
Prof Andrew Hanby, University of Leeds, UK
Prof Sarah Pinder, King's College London, UK
Prof Malcolm Reed, University of Sussex, UK
Dr Valerie Jenkins, University of Sussex, UK
Ms Maggie Wilcox, Independent Cancer Patients' Voice, UK

LORIS Trial Office

Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK

Enquiries:

☎ +44 (0) 121 414 3017
🖷 +44 (0) 121 414 8392
✉ LORIS@trials.bham.ac.uk

Patient Registration/Randomisation:

☎ +44 (0) 800 371 969 (9.00 am till 5.00 pm Monday to Friday)
☎ +44 (0) 121 414 7844 (9.00 am till 5.00 pm Monday to Friday)

Serious Adverse Event Reporting:

🖷 +44 (0) 121 414 8392
🖷 +44 (0) 121 414 7989

Diagnostic Slide Scanning

Dr Jane Steele
Human Biomaterials Resource Centre (HBRC), University of Birmingham, Birmingham, B15 2TT, UK
☎ +44 (0) 121 414 7668
✉ J.C.Steele@bham.ac.uk

Central Pathology Reviewers

Prof Andrew Hanby
Leeds Institute of Cancer and Pathology (LICAP), University of Leeds, Leeds, United Kingdom, LS9 7TF, UK
☎ +44 (0) 113 343 8431
✉ A.M.Hanby@leeds.ac.uk

Prof Sarah Pinder
Division of Cancer Studies, King's College London, 3rd Floor, Bermondsey Wing, Guy's Hospital Great Maze Pond, London, SE1 9RT, UK
☎ +44 (0) 020 7188 4260
✉ Sarah.Pinder@kcl.ac.uk

Dr Jeremy Thomas
Pathology Directorate, Western General Hospital, Edinburgh, UK
☎ +44 (0) 131 537 1961
✉ Jeremy.Thomas@nhs.net

Radiology Second Opinion Service

Prof Andrew Evans
Centre for Oncology & Molecular Medicine, Mail Box 4, Level 6 Centre for Oncology & Molecular Medicine, Division of Medical Sciences, University of Dundee, Dundee, DD1 9SY, UK
☎ +44 (0) 1382 383 014
✉ a.z.evans@dundee.ac.uk

Dr Matthew Wallis
Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK
☎ +44 (0) 1223 586 578
✉ Matthew.Wallis@addenbrookes.nhs.uk

Quality of Life Coordinating Centre

Miss Lucy Matthews
Sussex Health Outcomes, Research & Education in Cancer (SHORE-C), Brighton and Sussex, Medical School, University of Sussex, Falmer, Brighton, BN1 9RX, UK
☎ +44 (0) 1273 877 919
🖷 +44 (0) 1273 873 022
✉ L.Matthews@sussex.ac.uk

Translational Coordinating Centre

Mrs Carrie Cunningham and Prof John Bartlett
Biomarkers and Companion Diagnostics, Edinburgh Cancer Research Centre, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XR, UK
☎ +44 (0) 131 777 3570
🖷 +44 (0) 131 777 3520
✉ carrie.cunningham@igmm.ed.ac.uk

Mammographic Image Library

Dr Mark Halling-Brown
National Co-ordinating Centre for the Physics of Mammography, Medical Physics, Level B, St Luke's Wing, Royal Surrey County Hospital, Egerton Road, Guildford, GU2 7XX, UK
☎ +44 (0) 1483 571 122
✉ mhalling-brown@nhs.net

Sponsor

University of Birmingham, Birmingham, B15 2TT, UK

TRIAL SYNOPSIS

LORIS	The Low Risk DCIS Trial		
Chief Investigator	Miss Adele Francis		
ISRCTN No.	27544579	**Sponsor**	University of Birmingham, United Kingdom
Trial Design	A multi-centre, randomised (1:1), controlled phase III trial of Surgery versus Active Monitoring in patients with low risk ductal carcinoma *in situ* (DCIS), incorporating a 2 year internal Feasibility Study.		
Objectives of Feasibility Study	To demonstrate that a sufficient number of eligible patients can be identified and randomised over the course of the main trial, in order to answer robustly the study objectives. This will be evaluated from the following factors: • Number of sites open • Number of patients randomised • Mean monthly recruitment • Identified patient conversion rate • Number of eligible patients detected during screening • Patient consent to randomisation rate • Concordance rate of DCIS grade between initial assessment and Central Histopathology Review		

Primary Objective and Outcome Measures of Main Trial	
Primary Objective	To assess whether Active Monitoring is non-inferior to Surgery, in terms of ipsilateral invasive breast cancer free survival time
Outcome Measure	• Ipsilateral invasive breast cancer free survival time
Secondary Outcome Measures	• Time to development of ipsilateral invasive breast cancer • Time to development of any invasive breast cancer • Time to development of contralateral invasive breast cancer • Overall survival • Time to mastectomy • Time to surgery • Quality of Life (QoL) • Quality-Adjusted Life Years • Costs and cost-utility
Translational	An exploratory assessment of predictive biomarkers will be performed

Patient Population and Sample Size	932 women with confirmed low risk DCIS This is based on a non-inferiority margin defined as an absolute reduction in the 5 year ipsilateral invasive breast cancer free survival rate at 5 years of 2.5% i.e. from 97.5% to 95%

Key Entry Criteria

Inclusion

1) Female, aged ≥ 46 years
2) Screen-detected or incidental microcalcification
3) Histologically confirmed diagnosis of non-high grade DCIS confirmed by local pathologist (for both breasts if bilateral disease) by:
   Small volume core biopsy and Vacuum Assisted Core Biopsy (VACB)
   Or
   Vacuum Assisted Core Biopsy (VACB) alone as first line diagnostic approach
   Or
   Small volume biopsy or VACB plus open diagnostic surgical biopsy (without clear margins)
   Or

Open diagnostic surgical biopsy (without clear margins)

(in accordance with the current NHSBSP Guidelines for Pathology Reporting in Breast Cancer Screening)

4) DCIS diagnosed ≤90 days before registration
5) Bilateral DCIS is permitted if non-high grade DCIS is confirmed in both breasts at the time of mammogram and diagnostic biopsy
6) Able to give informed consent and comply with the trial schedule and completion of Patient Reported Outcome questionnaires
7) Patient fit and willing to undergo surgery
8) Written Informed Consent obtained

Exclusion

1) Previous or current diagnosis of invasive breast cancer or previous ipsilateral DCIS (previous surgically treated contralateral DCIS is permitted)
2) A mass lesion clinically on imaging at the site of the microcalcification which has not been proven on biopsy to be a specific benign lesion
3) Surgical procedure with curative intent (even if clear margins have not been achieved)
4) Unequivocal comedo necrosis observed
5) Any serious and/or unstable pre-existing condition that would prevent compliance with the trial or the consent process
6) Recent onset ipsilateral blood-stained nipple discharge without benign explanation
7) High risk group for developing breast cancer (as defined in current NICE guidelines for familial breast cancer (42), or due to prior exposure to mantle field radiotherapy)

Central Histopathology Review

All diagnostic histopathology slides will be submitted for central review as follows:

- Prior to randomisation to confirm low risk disease
- Following local confirmation of DCIS grade migration (from subsequent core biopsies in Active Monitoring Arm patients only)

The outcome of the central review will be made available within 1 week of receipt of the slides

Trial Assessments

Surgery Arm

- Annual mammography for a minimum of 10 years
- Patient Reported Outcomes (QoL and Health Economics) for 5 years
- Collection of follow-up data via annual follow-up appointment for years 1-5 and via annual telephone call to patient for years 6-10

Active Monitoring Arm

- Annual mammography for a minimum of 10 years
- Patient Reported Outcomes (QoL and Health Economics) for 5 years
- Collection of follow-up data via annual telephone call to patient for 10 years

Radiology Second Opinion Service

A radiological second opinion service is available upon request for Active Monitoring arm patients. The second opinion will be provided within 1 week of the request being made.

Translational Research

The following samples will be collected for translational research:

- Tumour blocks from diagnostic biopsies (all patients)
- Tumour blocks from surgical resection specimen (Surgery Arm patients)
- Tumour blocks from surgical resection specimen following disease progression (all patients)

Trial Duration

Recruitment 6 years (2 years Feasibility Study plus 4 years main trial)

Follow-up 10 years (extended follow-up data to be obtained via the Data Linkage Service)

CONTACT DETAILS

LORIS Trial Office

Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK

☎ +44 (0) 121 414 3017 🖷 +44 (0) 121 414 8392 ✉ LORIS@trials.bham.ac.uk

Quality of Life Coordinating Centre

Sussex Health Outcomes, Research & Education in Cancer (SHORE-C), Brighton and Sussex, Medical School, University of Sussex, Falmer, Brighton, BN1 9RX, UK

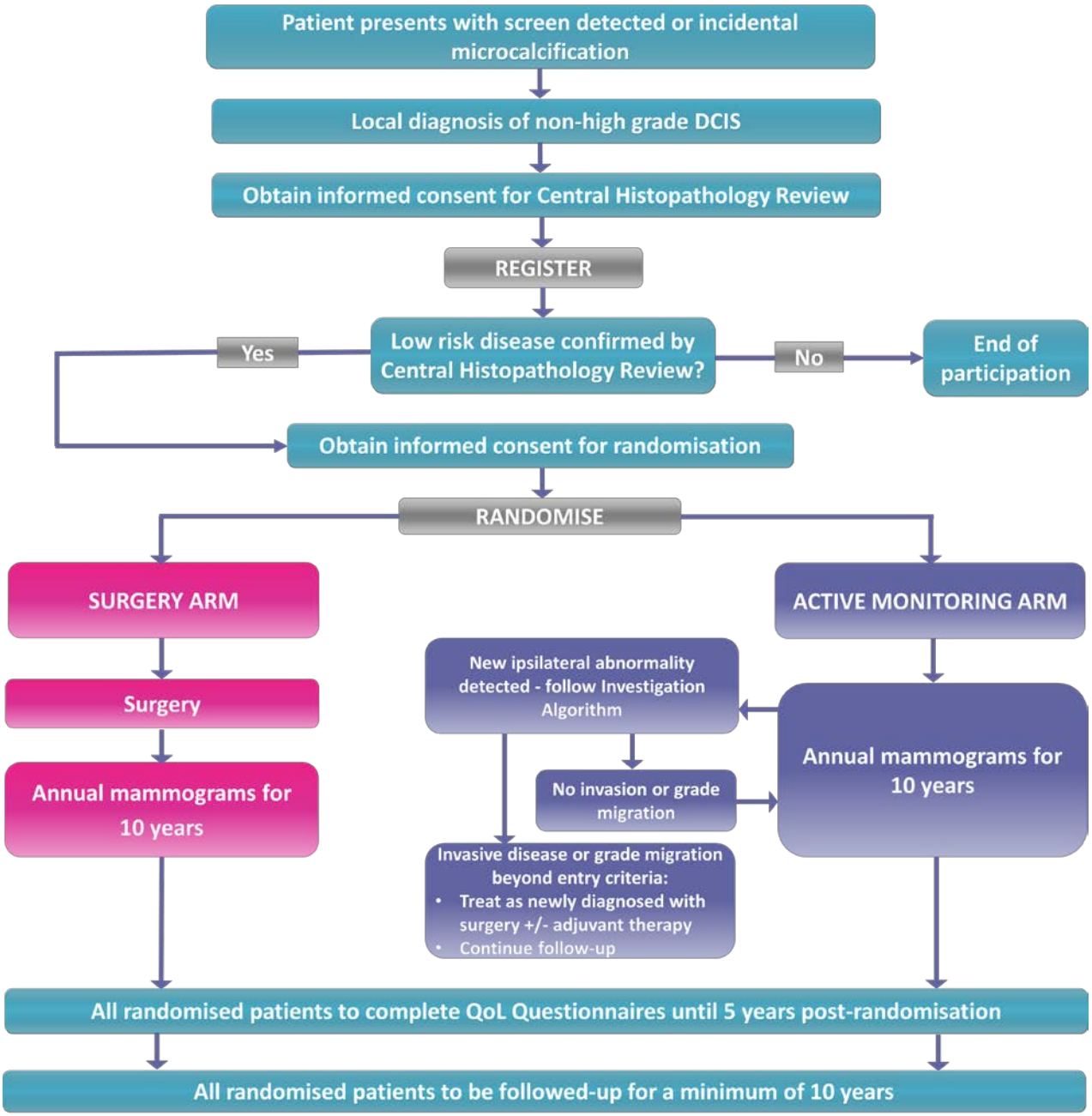
☎ +44 (0) 1273 877 919 🖷 +44 (0) 1273 873 022 ✉ L.Matthews@sussex.ac.uk

Translational Coordinating Centre

Biomarkers and Companion Diagnostics, Edinburgh Cancer Research Centre, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XR, UK

☎ +44 (0) 131 777 3570 🖷 +44 (0) 131 777 3520 ✉ carrie.cunningham@igmm.ed.ac.uk

Trial Schema



Schedule of Events:

Event	Pre-Randomisation: Screening	Low risk DCIS confirmed on Central Histopathology Review	Pre-Randomisation: Study Entry	On Study: Post-Randomisation	Patients allocated to Surgery Arm undergo surgery within 60 days of diagnosis	On Study: Annual Follow-up Years 1 - 5	Long Term Follow-Up: Annual Follow-Up Years 6-10
Local diagnosis of non-high grade DCIS (small volume biopsy plus VACB, or first line VACB, or small volume biopsy or VACB plus open diagnostic surgical biopsy without clear margins or open diagnostic surgical biopsy without clear margins (alone)	X						
Medical history	X						
Confirmation of eligibility	X						
Informed consent for registration	X						
Registration	X						
All diagnostic slides submitted for Central Histopathology Review	X						
Informed consent for randomisation			X				
Patient completes baseline QoL questionnaires and Accept/Decline questionnaire[$]			X				
Randomisation			X				
Baseline details				X			
Treatment Endocrine therapy/radiotherapy initiated in accordance with local practice				X			
Primary tumour sample collection Diagnostic biopsy (all patients) Surgical specimen (Surgery Arm patients only)				X			
Patient Reported Outcomes QoL questionnaires at: 3 months, 6 months and annually Patient Costs Questionnaire at 1 random time point				X		X	
Annual follow-up Mammography (all patients)						X	X
Annual clinic visit or telephone call to patient (Surgery Arm only)						X	
Annual telephone call to patient (Active Monitoring Arm only)						X	
Annual telephone call to patient (all patients)							X
Investigations and treatment of ipsilateral disease (Active Monitoring Arm only)* Biopsy in accordance with Investigation Algorithm Submit diagnostic slides for Central Histopathology Review Surgery and other treatment for disease progression or new breast disease				As required		As required	As required
Tumour sample collection Tumour blocks for disease progression or new breast disease				X		X	X
Related Adverse Event review				X		X	
Reporting of: survival, disease progression, development of new breast disease				In real time		In real time	In real time

[$] Completed during Feasibility Study only. Note that during the Feasibility Study, a proportion of eligible, consenting patients will also be contacted for telephone interview by SHORE-C.

* Patients in the surgery arm will treated in accordance with local practice.

ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALH	Atypical Lobular Hyperplasia
CRF	Case Report Form
CRCTU	Cancer Research UK Clinical Trials Unit
CWT	Cancer Waiting Times
DMC	Data Monitoring Committee
DCIS	Ductal Carcinoma *in situ*
ER	Oestrogen Receptor
GCP	Good Clinical Practice
H&E	Haematoxylin and Eosin
HER-2	Human Epidermal Growth Factor Receptor 2
HBRC	Human Biomaterials Resource Centre
HRT	Hormone Replacement Therapy
ICPV	Independent Cancer Patients' Voice
ISF	Investigator Site File
NCI	National Cancer Institute
NCCPM	National Co-ordinating Centre for the Physics of Mammography
NHS	National Health Service
NHSBSP	National Health Service Breast Screening Programme
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
PgR	Progesterone Receptor
PRO	Patient Reported Outcome
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
SAE	Serious Adverse Event
SHORE-C	Sussex Health Outcomes Research & Education in Cancer
SS&DL	Site Signature and Delegation Log
STAI	State/Trait Anxiety Inventory
TMG	Trial Management Group
TNO	Trial Number
TSC	Trial Steering Committee
UK	United Kingdom
USS	Ultrasound Scan
VACB	Vacuum Assisted Core Biopsy

TABLE OF CONTENTS

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Breast Screening, Overdiagnosis and Overtreatment

The introduction of mammographic breast screening in the United Kingdom (UK) has resulted in a dramatic increase in the diagnosis of Ductal Carcinoma *in situ* (DCIS) (1-3). This is increasing with the current rollout of digital mammography, which is a more sensitive technique for detecting microcalcification, compared to standard film screen mammography. The increased incidence of DCIS represents an increasing burden on National Health Service (NHS) resources. In 2009-2010, 2,830 women were diagnosed with *in situ* carcinoma through the NHS Breast Screening Programme (NHSBSP) (4). Screen-detected DCIS now accounts for 20% of 'cancers' identified through breast screening, however, the intent of breast screening programmes was to detect early invasive cancer, not to detect DCIS. The large rise in DCIS diagnoses has not been accompanied by a corresponding fall in the incidence of invasive cancers, as would be expected if DCIS inevitably leads to invasive cancer, despite the length of follow-up now available from the NHSBSP. Analysis is confounded by a rising background incidence and other factors clearly play a role but it is far from clear that diagnosing and treating asymptomatic DCIS with surgery saves lives.

'Overdiagnosis' refers to diagnosing healthy women with cancer who would never otherwise have presented with a symptomatic breast cancer diagnosis in their lifetime and is not confined to the screened population. The degree of overdiagnosis of DCIS is the subject of increasingly polarised debate and growing clinical concern, particularly the belief that women are not being given an opportunity to make an informed choice. At present, all DCIS is treated by surgery because it is not known which cases would not progress in the woman's lifetime to a life threatening invasive tumour. The inevitable consequence of overdiagnosis is 'overtreatment'. The numbers 'over-treated' are the subject of contention (5) but there is general recognition that overtreatment exists.

The current treatment of screen detected but otherwise asymptomatic DCIS, leads to a diagnosis of 'cancer', followed by surgery, various adjuvant treatments and long term follow-up with associated anxiety. In the UK, 30% of women diagnosed with screen-detected *in situ* cancer (non-invasive or microinvasive) are treated by mastectomy and 70% by breast conservation surgery. This compares with 26% of women with screen-detected invasive cancer who are treated by mastectomy. The management of DCIS within the NHS is a multidisciplinary effort consuming considerable health care resources in breast radiology, surgery, radiotherapy and out-patient follow-up. It clearly unnecessarily exposes many women not just to the morbidity of treatment but also to the lifelong anxiety associated with it. It is appropriate now to address these economical and ethical issues through prospective randomised trials.

The majority of DCIS detected is high grade. There is recognition that high grade DCIS is more likely to progress, if untreated, to an invasive cancer although direct evidence for this is lacking. Recently published UK screening data (6) show the differential effect of DCIS grade on type of recurrence and time to invasive recurrence supports the model suggesting that breast cancer evolves along two distinct molecular genetic pathways (7, 8), particularly as no high-grade recurrences, metastatic events or deaths were identified from the cohort of low grade DCIS. If this trial showed that it was safe to leave all low risk DCIS untreated, approximately 1000 (including NHSBSP and non-screen detected) patients a year in the UK could safely avoid surgery and adjuvant treatment. If non-inferiority is shown, this trial will be practice changing with the associated cost savings and reduction in surgery.

An independent patient advocate group (Independent Cancer Patients' Voice) whose aim is to improve existing treatments for every cancer patient by bringing the patients' voice into clinical research have been involved in the study since conception and have provided a direct patient perspective throughout the LORIS Trial, assisting in the development of patient material and in creating awareness of the trial.

The LORIS trial will enable women to make a better-informed choice about their options if diagnosed with low risk DCIS. Some of the data will not be available for many years but this is not a trial that can become clinically irrelevant or be answered in any other way.

The radiological, pathological and translational data from this trial will enable better future selection of those patients who can safely avoid surgery.

Women will be able to make appropriate choices based on the chances of invasive disease developing in their breast post low risk DCIS diagnosis and over what timescale. The published evidence (6) suggests that the current interruption of women's lives for urgent and often major surgical 'cancer' treatment within 31 days of diagnosis of low risk DCIS is unnecessary, inappropriate and misleading for the recipient. This urgent

treatment must be a contributing factor to the patient's perception of the risk of dying from their disease being similar to that of patients with invasive disease (9).

The Benefits and Harms of Breast Screening; An Independent Review was commissioned by the Department of Health to address these issues of debate and was published in full in 2013 (10). They found benefits and harms of the programme and importantly established that screening saves lives but also that over diagnosis exists. The panel estimated that for 10,000 UK women invited to screening from age 50 for 20 years, about 681 cancers will be found, of which 129 will represent overdiagnosis, and 43 deaths from breast cancer will be prevented. In round terms therefore, for each breast cancer death prevented, about three overdiagnosed cases will be identified and treated.

The panel's review of overdiagnosis lead to their recommendation for further research into DCIS, in particular this proposed study to examine the need for treatment of low grade DCIS.

1.1.2 Omitting Surgery for Ductal Carcinoma in situ

Until recently, there has been minimal data on the natural history of non-operated DCIS and what published data there is refers to retrospective reviews of missed diagnoses. They relate to an era of very different qualities of imaging and biopsy and do not include active monitoring by mammography. The patients described in these series would not be eligible for the LORIS trial and almost all presented symptomatically:

- Sanders *et al*. (11) identified 28 women with low grade DCIS treated by biopsy only in the 1950s and 1960s. Biopsies were originally reported as benign. All patients were symptomatic, and thus none would be eligible for this trial. Large volume biopsies were not available at that time and this small, retrospective cohort were all originally misdiagnosed as benign lesions. At 10 years 71% (n=20) of patients had not developed an ipsilateral invasive breast cancer i.e. 29% patients (n=8) developed breast cancer within 10 years and 4 more (14%) were diagnosed between 10 and 42 years.
- Betsill *et al*. (12) reported the outcome of 25 patients with symptomatic low grade DCIS treated by biopsy alone, with a mean follow-up of 21.6 years; 7 had developed invasive carcinoma at an average interval of 9.7 years (range of 7 to 30 years). None would have been eligible for this trial.
- A lower invasion rate was reported by Eusebi *et al.* (13), when 11 of 80 women with DCIS treated with biopsy alone developed invasive carcinoma at a mean follow-up of 17.5 years. This retrospective data is not applicable to current DCIS classification.
- The Nurses' Health Study (14) showed that of 13 patients with low grade DCIS 'treated' by biopsy alone, 2 developed invasive carcinoma (at 5 and 18 years post-biopsy).

These data, albeit numerically small, retrospective and based primarily on misdiagnoses of symptomatic patients nevertheless suggest that the inclusion criteria for this first trial of active monitoring should be mammogram-detected, asymptomatic, with central pathology reviewed low risk DCIS and that long term mammographic follow up is required. For clarification however, the patients in the series stated above would not be eligible for this trial, due to symptomatic presentation.

Sagara *et al.* (15) recently published data from a study designed to investigate if there was a survival benefit offered by the surgical management for low-grade ductal carcinoma in situ of the breast. The study indicated that there was no survival benefit. This was a retrospective longitudinal cohort study using the Surveillance, Epidemiology, and End Results database from October 9, 2014, to January 15, 2015, at the Dana-Farber/Brigham Women's Cancer Center. Between 1988 and 2011, 57 222 eligible cases of DCIS with known nuclear grade and surgery status were identified. Patients were divided into surgery and non surgery groups. Propensity score weighting was used to balance patient backgrounds between groups. A log-rank test and multivariable Cox proportional hazards model was used to assess factors related to overall and breast cancer–specific survival. Of the 57, 222 cases of DCIS identified in this study, 1169 (2.0%) were managed without surgery and 56, 053 cases (98.0%) were managed with surgery. Multivariable analysis showed there was no significant difference in the weighted hazard ratios of breast cancer specific survival or overall survival between the surgery and non-surgery groups for low-grade DCIS. A higher proportion of patients in the USA have a diagnosis of low grade DCIS compared to that of the UK. This USA population of low grade patients is likely to be the equivalent of our low and low-intermediate grade patients.

1.1.3 Classification of Ductal Carcinoma in situ and Consistency of Categorisation

Data from The Sloane Project, a UK audit of screen-detected DCIS including over 10,000 cases, gives the following grade distribution: high 66%; intermediate 25%; low 9% (16). It is well recognised that grading of DCIS by pathologists is inconsistent, as shown in the NHSBSP pathology EQA scheme (17). Therefore, all locally diagnosed low and intermediate grade biopsies will be centrally reviewed. Those deemed "Low Risk" (defined as low grade and at the boundary between low and intermediate grade) will be eligible for randomisation. This eligibility criterion is based both on the results of the UK DCIS 1 Trial (18) which, from central review, showed comparable local recurrence following low and intermediate cytonuclear grade DCIS (Hazard Ratios of 0.51 and 0.41 respectively compared to high grade disease) and the proven inconsistency of reporting at the boundary of low and intermediate grade. If future pathological classification changes to describe high grade and non-high grade DCIS based on robust reproducible criteria rather than the current subjective low/intermediate/high, then the role of active monitoring in the entire non-high grade group may be considered. However, wide discussion has provided consensus that, currently, for surgical equipoise the inclusion criteria for this first assessment of no surgery should be targeted only at low grade and those intermediate grade lesions with some low grade features.

Until recently, diagnosis of DCIS was predominantly made using small volume biopsies i.e. 14-gauge, however large volume Vacuum Assisted Core Biopsy (VACB) 11-gauge and 8-gauge is now standard for low suspicion microcalcifications and is in widespread use in the UK. VACB provides a larger tissue sample and improves both the accuracy of diagnosis of DCIS grade and greater assurance of the absence of invasion (19, 20), hence the utilisation of this technique in this trial.

1.1.4 Microcalcification Morphology

Appearances of microcalcification are not a good indicator of grade and relate more to the extent of disease (21). The Sloane Project has also shown that lesion size is a major determinant of the mammographic features of DCIS. Radiological morphology has not been included as either a restriction to trial entry or a rationale for patient recall.

A single paper from Meyerson *et al.* (22) retrospectively reviewed mammographic changes in 14 patients who were treated with endocrine therapy alone. Six women in whom radiological change precipitated surgical intervention had increasing microcalcification, developing asymmetry or a new mass lesion.

1.1.5 Endocrine Therapy for Surgically Treated Ductal Carcinoma in situ

There is evidence from one placebo-controlled trial, NSABP B-24 (23), that in patients treated for DCIS with lumpectomy and adjuvant radiotherapy, tamoxifen reduces the risk of ipsilateral local recurrence by 30% and of contralateral breast cancer by 50% (24). The absolute risk at 5 years of any (invasive or non-invasive) breast cancer event is small (tamoxifen arm 8% and placebo arm 13%). Survival was not influenced by treatment. A subsequent randomised controlled trial with a more complex design (25, 26) examined the use of tamoxifen versus no adjuvant therapy following complete local excision of DCIS in the absence or presence of radiotherapy. In the absence of radiotherapy, tamoxifen was again associated with a 30% overall reduction in breast events through reduction in DCIS recurrence and contralateral DCIS and invasive disease events. Tamoxifen was however ineffective in preventing ipsilateral invasive recurrence. In the presence of radiotherapy, tamoxifen appeared ineffective. Survival was not impacted by radiotherapy or tamoxifen in this trial, with breast cancer accounting for only 20% of all deaths (2% breast deaths and 11% overall deaths).

Recent data from two trials (IBIS II DCIS and NSABP B-35) comparing tamoxifen and the aromatase inhibitor anastrazole have reported no difference or a slight reduction in breast cancer events with anastazole. No survival differences have been observed but follow up is short (27, 28).

National Institute for Health and Care Excellence (NICE) guidelines for familial breast cancer state "Do not offer adjuvant tamoxifen after breast conserving surgery to patients with DCIS" (29).

There is sparse data regarding endocrine treatment alone for DCIS. Data presented at the San Antonio Breast Cancer Symposium in 2011 showed a decrease in subsequent breast events in patients with all types of atypia, including DCIS. This was a retrospective study, including symptomatic patients and was not restricted to large volume biopsies (30). The role of endocrine therapy in asymptomatic, surgically untreated, low risk DCIS, remains unknown and of unproven long term utility. Endocrine therapy is associated with significant and persistent side effects.

1.1.6 Follow-up Data

The evidence for mammographic follow-up for invasive breast cancer and DCIS is limited. A Health Technology Assessment (HTA) sponsored meta-analysis (31) showed that follow-up regimens that included regular mammograms offer a survival benefit over those that did not. How long follow-up should continue is still subject to debate (21) and there are widespread differences in UK practice (32). However, given that the DCIS treatment and observational trials (23) all show that events continue to occur long term it would seem appropriate to continue active monitoring with annual mammography for at least 10 years before entering back into the NHSBSP.

1.1.7 Translational Science

A huge diversity of biological variation in invasive cancers is recognised but for DCIS is largely restricted to small studies of 'conventional markers' of invasive disease. There are an ever-increasing number of potential 'biomarkers' for invasive cancers but translational research into DCIS lags significantly behind. Categorisation of DCIS is routinely based predominantly on cytonuclear grade. The validity of grading of DCIS is reinforced by studies of biological markers; high grade DCIS is often positive for Human Epidermal Growth Factor Receptor 2 (HER-2) and p53 and tends to be negative for oestrogen receptor (ER), Progesterone Receptor (PgR) and bcl-2, with a high proliferation rate. Conversely, low grade DCIS is typically negative for HER-2 and p53, positive for ER, PgR and bcl-2, and has a low proliferation rate (33) (34). There are also genetic differences between different grades of DCIS indicating that these are truly different pathways to the progression of invasive carcinoma (35, 36). However, to date, none of these individual markers have proven efficacy in distinguishing between rates of recurrence, either of invasive or non-invasive disease. The processes involved in progression of DCIS to invasive disease are poorly understood. Most retrospective studies are under-powered and based on the premise that markers of prognosis in invasive cancer (e.g. HER-2, ER, Ki67) may predict recurrence in DCIS. Some evidence suggests these markers are prognostic in DCIS, however, until very recently, no reliable evidence existed to identify markers of invasive recurrence following an initial diagnosis of DCIS. There have been multiple challenges that act as barriers to effective and high quality translational research on DCIS. These include poor standardisation of pathology assessment, small samples, comparable fixation of all tissue for diagnosis, incomplete follow up, low event rates and lack of distinction between invasive versus DCIS recurrence in some of the published literature. Each of these, individually, restricts progress in this field. Within the LORIS trial, we are presented with a unique opportunity to surmount each of these obstacles, particularly when linked to advances in current technology that allow the analysis of gene expression from very small quantities of DNA/RNA (100-200ng) or from micro-dissected samples of 100-1000 cells.

The paucity of existing data on predictive biomarkers of invasion following a primary diagnosis of low risk DCIS makes it challenging to identify specific markers or marker panels which can be prospectively validated within the LORIS trial at present. However, experience has shown that progress in this field is rapid and the technological developments outlined above will provide impetus to this field.

Clearly, there is a need for research in this area to avoid inappropriately selecting DCIS cases with high risk of progression for observation rather than surgery. The biobanking of samples from the LORIS trial will provide a unique future resource for such studies and is regarded as an essential component of the study. By collecting samples for future analysis, we will secure a unique resource to allow such markers to be developed in future.

1.1.8 Psychosocial Aspects

The diagnosis of DCIS can provoke significant psychological distress; confusion about the seeming ambiguity of having "a very early form of breast cancer" with no manifest tumour, yet requiring treatments that may include mastectomy (37). Most published research is cross sectional comparing outcomes of women with DCIS and those with invasive breast cancer (9, 38).

Some research suggests that women treated for DCIS may have better physical, sexual, and social functioning than those with invasive breast cancer (32). However, despite the relatively good prognosis, one study showed that DCIS patients appeared to hold similar perceptions about the risks of recurrence and of dying as women with early invasive breast cancer. They also fear disease spreading to other parts of the body and these inaccurate perceptions changed little over 18 months (39, 40). At least two studies report psychological distress in DCIS to be similar to that found in women with invasive cancer (41).

Quality of Life (QoL) is a secondary outcome of the main trial and will provide unique insight and direction into the successful management of this condition.

1.2 Trial Rationale

1.2.1 Justification for Patient Population

The patient population are women of NHSBSP age or above (as these women can still access the screening programme) who have had their asymptomatic DCIS detected by mammogram. Outside of this age group, mammograms in the absence of symptoms are rarely performed and, consequently, the diagnosis of low and intermediate grade DCIS is also rare. Patients with high grade DCIS are excluded from this trial.

Men are not screened for breast cancer, very rarely have mammograms and are rarely diagnosed with DCIS.

To include patients diagnosed locally as having Atypical Ductal Hyperplasia or similar would potentially over-treat a population that is not currently being over-treated. However, if the local pathologist has reported a case as low grade DCIS and the Central Histopathology Reviewers deem the sample to represent ADH or similar the patient will still be considered eligible for randomisation. This pragmatism is required to ensure that the trial reflects current clinical practice. The only patients that the central review process will exclude are those with high risk disease.

To include low grade screen-detected invasive disease in this initial trial design is a step further than the wider surgical community might currently be prepared to accept.

1.2.2 Justification for Design

It is appropriate to address the issue of overtreatment of DCIS through a prospective randomised trial. Data from trials which have addressed the need for radiotherapy following breast conservation treatment do not contain many patients with low grade DCIS diagnosed with large volume biopsy, but do suggest that if low grade DCIS recurs as invasive cancer the cancer is also low grade and occurs much later than recurrence related to high grade DCIS e.g. NSABP-B17 (23). There is widespread concern amongst patient representative groups that the question of which women with DCIS diagnoses can safely avoid surgery is not being addressed within a contemporary prospective clinical trial and informed choice is therefore not currently possible. There is similar concern amongst many clinicians that adequate advice cannot be given to patients regarding overtreatment, as it has never been addressed. The clinical community has concentrated until now on discussing the degree of overtreatment (e.g.www.breastcancercare.org.uk/forum/dcis-lcis-f21.html). There is no relevant, published QoL data to demonstrate the harms and/or benefits of current practice.

1.2.3 Choice of Treatment

The experimental arm of the LORIS trial is necessarily Active Monitoring alone, to answer the trial question of whether low risk DCIS is being overtreated, with healthy women undergoing unnecessary cancer treatment.

2 AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Feasibility Study

2.1.1 Aims and Objectives

The aim of the Feasibility Study is to demonstrate that a sufficient number of eligible patients can be identified and recruited over the course of the main trial, in order to answer robustly the study objectives. This will be evaluated from the following factors:

- Number of sites open and randomising patients
- Number of patients randomised
- Mean monthly recruitment
- Identified patient conversion rate
- Number of patients with low or intermediate grade DCIS detected during screening for the LORIS Trial
- Patient consent to randomisation rate
- Concordance rate of DCIS grade between initial assessment and Central Histopathology Review

2.1.2 Outcome Measures

- Number of sites open and randomising patients: defined as the total number of sites activated for registration with at least 1 patient randomised at the end of year 2
- Number of patients randomised: total number of patients randomised from all randomising sites during the feasibility phase
- Mean monthly recruitment: defined as the average (mean) monthly number of patients randomised from all randomising sites involved in the Feasibility Study in total (not per site) during the final 4 months of the feasibility phase only (months 21-24)
- Identified patient conversion rate: defined as the number of randomised patients as a proportion of the number of patients identified as having low or intermediate grade DCIS and invited to take part during the final 4 months of the Feasibility Study only (months 21-24)
- Number of patients with low or intermediate grade DCIS detected during screening for the LORIS Trial: defined as the total number of patients with low or intermediate grade DCIS identified through Patient Screening/Enrolment Logs over the course of the Feasibility Study for all sites
- Patient consent to randomisation rate: defined as the percentage of patients consenting to randomisation during the Feasibility Study as a proportion of all patients identified as eligible for randomisation from Central Histopathology Review
- Concordance rate of DCIS grade between initial assessment and Central Histopathology Review: defined as the number of patients whose initial assessment of low or intermediate grade DCIS is confirmed by Central Histopathology Review, as a proportion of all samples reviewed during the Feasibility Study

2.2 Main Trial

2.2.1 Aims and Objectives

The aim of the main trial is to determine whether women with newly diagnosed low risk DCIS can safely avoid surgery, without detriment to their psychological well-being and can those patients who do require surgery be identified by pathological and radiological criteria.

2.2.1.1 Primary Objective

To assess whether Active Monitoring is non-inferior to Surgery, in terms of ipsilateral invasive breast cancer free survival.

2.2.1.2 Secondary Objectives

- Time to development of ipsilateral invasive breast cancer
- Time to development of any invasive breast cancer
- Time to development of contralateral invasive breast cancer
- Overall survival
- Time to mastectomy
- Time to surgery
- Quality of Life
- Quality-Adjusted Life Years (QALY)
- Costs and cost-utility

2.2.1.3 Translational Objectives

An exploratory assessment of predictive biomarkers will be performed

2.2.2 Outcome Measures of Main Trial

2.2.2.1 Primary Outcome

Ipsilateral invasive breast cancer free survival time: defined in whole days measured as time from randomisation until first report of ipsilateral invasive breast cancer or death (from any cause), whichever happens first. Patients who withdraw or who are lost to follow-up will be censored at the date last known to be alive and free of disease. Patients not having an event at the time of analysis will be censored at the date last seen alive and free of disease.

2.2.2.2 Secondary Outcomes

- Time to development of ipsilateral invasive breast cancer: defined in whole days measured as time from randomisation until first report of ipsilateral invasive disease. Randomised patients with no evidence of disease will be censored at the last reported follow-up
- Time to development of any invasive breast cancer: defined in whole days measured as time from randomisation until first report of any invasive disease. Randomised patients with no evidence of disease will be censored at the last reported follow-up
- Time to development of contralateral invasive breast cancer: defined in whole days measured as time from randomisation until first report of contralateral invasive disease. Randomised patients with no evidence of disease will be censored at the last reported follow-up
- Overall survival time: defined in whole days measured as time from randomisation to date of death from any cause. Patients who withdraw or who are lost to follow-up will be censored at the date last known to be alive. Patients who remain alive during the course of the study will be censored at the date last seen alive
- Time to mastectomy: defined in whole days measured as the time from randomisation until time of mastectomy surgery. All other patients will be censored at last know follow-up assessment having not had a mastectomy

- Time to surgery: defined as time in whole days measured from randomisation until first reported ipsilateral breast cancer/DCIS related surgery. All other patients will be censored at last known follow-up assessment having not received surgery
- Quality of Life: will be assessed using the following:

  Brief COPE

  Spielberger State-Trait Anxiety Inventory

  SF-36v2 Health Survey

  Euro Qol EQ-5D

- Quality-adjusted Life years (QALY): survival time and longitudinal measures of EQ-5D will be combined to form a QALY outcome
- Costs and cost-utility: per-patient costs will be calculated from Patient Costs Questionnaires and utilising clinical data and key resource use data from Case Report Forms (CRFs), enabling economic evaluation of clinically important outcomes such as cost per additional surgical treatment avoided and cost per diagnosis of ipsilateral breast cancer and cost per QALY

3 TRIAL DESIGN

LORIS is a multi-centre, randomised (1:1), controlled phase III trial of surgery versus active monitoring in patients with low risk DCIS, incorporating a 2 year internal Feasibility Study, designed to answer the following question:

> Can women with newly diagnosed low risk DCIS safely avoid surgery, without detriment to their psychological well-being and can those patients who require surgery be identified by pathological and radiological criteria?

Patients diagnosed locally with non-high grade DCIS will be registered with the Trial Office in order for the Central Histopathology Review team to verify that the patient has low risk disease. Patients with confirmed low risk disease will then be randomised to Surgery or Active Monitoring.

The LORIS Trial will seek to randomise 932 women with low risk disease. This is based on a non-inferiority margin defined as an absolute reduction in the 5 year ipsilateral invasive breast cancer free survival rate at 5 years of 2.5% i.e. from 97.5% to 95%.

4 ELIGIBILITY

The following criteria are applicable in order for a patient to be registered into the study. Patients will only be deemed eligible for randomisation following confirmation of low risk disease by the trial's Central Histopathology Review team.

4.1 Inclusion Criteria

1) Female, aged ≥ 46 years
2) Screen-detected or incidental microcalcification
3) Histologically confirmed diagnosis of non-high grade DCIS confirmed by local pathologist (for both breasts if bilateral disease) by:

   Small volume core biopsy and Vacuum Assisted Core Biopsy (VACB)

   Or

   Vacuum Assisted Core Biopsy (VACB) alone as first line diagnostic approach

   Or

   Small volume biopsy or VACB plus open diagnostic surgical biopsy (without clear margins)
   Or

Open diagnostic surgical biopsy (without clear margins)

(in accordance with the current NHSBSP Guidelines for Pathology Reporting in Breast Cancer Screening)

4) DCIS diagnosed ≤90 days before registration
5) Bilateral DCIS is permitted if non-high grade DCIS is confirmed in both breasts at the time of mammogram and diagnostic biopsy
6) Able to give informed consent and comply with the trial schedule and completion of Patient Reported Outcome questionnaires
7) Patient fit and willing to undergo surgery
8) Written informed consent obtained

4.2 Exclusion Criteria

1) Previous or current diagnosis of invasive breast cancer or previous ipsilateral DCIS (previous surgically treated contralateral DCIS is permitted)
2) A mass lesion clinically on imaging at the site of the microcalcification which has not been proven on biopsy to be a specific benign lesion
3) Surgical procedure with curative intent (even if clear margins have not been achieved)
4) Unequivocal comedo necrosis observed
5) Any serious and/or unstable pre-existing condition that would prevent compliance with the trial or the consent process
6) Recent onset ipsilateral blood-stained nipple discharge without benign explanation
7) High risk group for developing breast cancer (as defined in current NICE guidelines for familial breast cancer (42), or due to prior exposure to mantle field radiotherapy)

5 SCREENING AND CONSENT

Please see Flowchart 1: Patient Pathway to Randomisation, later in this section.

5.1 Involvement of Local Breast Unit or Screening Unit

It is expected that the majority of patients enrolling in the trial will have recently attended their local Breast Unit or Screening Unit.

Where possible, the Breast Unit or Screening Unit should supply potential patients with a copy of the brief Patient Information Leaflet, either with the invitation to attend for assessment or when attending for a biopsy.

5.1.1 Patient Information Leaflet

The aim of the Patient Information Leaflet is to describe DCIS to potential LORIS participants and to prepare the patient for the possibility of being invited to take part in a research study at an early stage in the patient pathway.

It is recognised from the experiences of the HTA funded ProTECT Trial that patients who are provided with trial information prior to learning of their diagnosis are more receptive and inclined to enter a clinical trial than those patients that have not received any trial information.

The LORIS Patient Information Leaflet has been carefully constructed with the assistance of Independent Cancer Patients Voice (ICPV) and has been ethically approved for use prior to the patient's diagnosis. Whilst it is appreciated that the information is provided to patients at a very early time-point and may not be relevant to all patients, patient interviews conducted during the feasibility phase of the LORIS Trial by the SHORE-C team indicated that patients are receptive to receiving the information at this stage in the pathway.

5.2 Local Diagnosis of Non-high Grade Ductal Carcinoma *in situ*

Diagnosis of non-high grade DCIS by VACB of a minimum of 12-gauge or open diagnostic surgical biopsy without clear margins is a pre-requisite for trial entry. The number of core samples required depends upon the size of the area of radiological abnormality but for the majority of patients a minimum of six cores is recommended. Microcalcification should be present on specimen radiography and a marker clip should be inserted at the time of VACB or open diagnostic surgical biopsy. Use of USS visible biopsy site markers is recommended. The NHSBSP Assessment Guidelines for sampling should be followed. If the calcification is extensive and the intended surgery would be mastectomy (should the patient be allocated to the Surgery Arm), taking biopsies from more than one area is recommended.

All specimens should be immediately fixed in 10% buffered formalin and processed as per local practice, through to paraffin wax embedded material. In accordance with NHSBSP Publication 50: Guidelines for Non-operative Diagnostic Procedures and Reporting in Breast Cancer Screening (43), at least 3 Haematoxylin and Eosin stained (H&E) slides ('levels') of the biopsy specimens should be examined.

All slides should be submitted for review along with any additional ER and/or immunohistochemistry diagnostic slides that have been performed (please refer to section 6.1.3).

DCIS grade will first be ascertained by the local pathologist, in accordance with NHSBSP Publication 58: Guidelines for Pathology Reporting in Breast Disease (44).

All patients diagnosed with non-high grade DCIS by small volume core biopsy and VACB (12-gauge or larger) or VACB or small volume biopsy or VACB plus open diagnostic surgical biopsy (without clear margins) or open diagnostic surgical biopsy (without clear margins) who meet the eligibility criteria specified, may be approached about the trial and consented for registration (see Section 5.5. Informed Consent).

If a patient has been diagnosed locally with non-high grade DCIS by small volume biopsy only (14-gauge or by a 13-gauge hand-held device), they should be invited to consent to and undergo a VACB as part of their registration into the study, to confirm the local diagnosis of non-high grade DCIS. If local reporting confirms non-high grade DCIS, all of the histology slides from all biopsies should then be submitted for Central Histopathology Review (see Section 6.1.3 Submitting Slides for Central Histopathology Review).

Patients diagnosed with non-high grade DCIS by open diagnostic surgical biopsy who meet the eligibility criteria specified, may be approached about the trial and consented for registration. These patients will not need to undergo a VACB procedure.

5.3 Screening

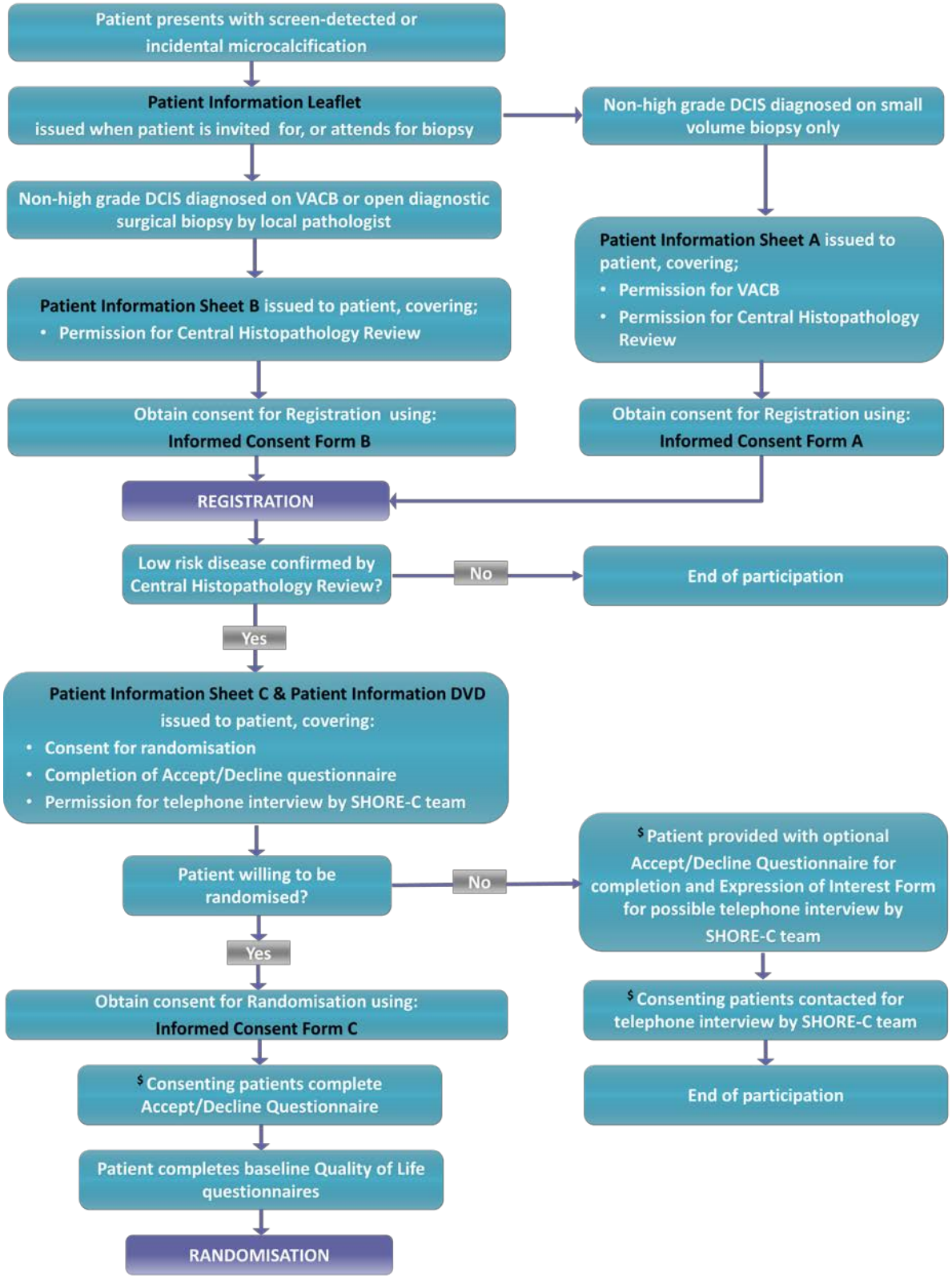
Potential patients will be identified via clinic referrals from Breast Units or Screening Units or from Multi-disciplinary Team meetings.

The screening requirements defined in this protocol are standard practice in many sites and can therefore be commenced prior to obtaining trial consent. However, if diagnosis or confirmation of diagnosis by VACB does not form part of standard practice for this group of patients at an individual site, informed consent (see Section 5.5 Informed Consent) should be obtained prior to VACB being performed.

Breast Units or Screening Units should adhere to their own policy regarding USS, however, USS is recommended for patients with dense breasts or focal asymmetry associated with the calcification on mammography.

The Patient Screening/Enrolment Log should be completed for all patients considered for the trial. During the Feasibility Study, the Trial Office will request a copy of the Patient Screening/Enrolment Log on a monthly basis.

5.4 Flowchart 1: Patient Pathway to Randomisation



$Applicable during Feasibility Study only. Randomised patients who consent to the telephone interview may be contacted shortly after randomisation by a member of the SHORE-C team.

5.5 Informed Consent

It is the responsibility of the Investigator or delegate to obtain written informed consent for each patient prior to performing any trial related procedure. The Investigator may delegate responsibility for obtaining written informed consent to other appropriate members of the site research team, for example Consultant Radiologists, Radiographers, Clinical Nurse Specialists and Research Nurses who are appropriately trained in obtaining informed consent and in Good Clinical Practice (GCP). Delegation of responsibility for obtaining written informed consent must be indicated appropriately on the Site Signature and Delegation Log (SS&DL).

Patient consent will be undertaken in two stages for all patients randomised into the trial; consent for registration (to allow Central Histopathology Review of all of the diagnostic slides) followed by consent for randomisation. There are three different Patient Information Sheets (A, B and C) and corresponding Informed Consent Forms (A, B and C) for this purpose (see previous Flowchart 1: Patient Pathway to Randomisation).

Patient Information Sheet A is intended for those patients who have been diagnosed locally via small volume biopsy only. The information sheet covers both the additional investigation of VACBs plus subsequent Central Histopathology Review of all of the diagnostic slides in the event that the VACBs confirm the local diagnosis of low or intermediate grade DCIS when reviewed by the local pathologist.

Patient Information Sheet B is intended for those patients who have been diagnosed locally via VACB or by open diagnostic surgical biopsy (with or without prior small volume biopsies or VACBs). This information sheet covers the Central Histopathology Review.

Following confirmation of patient eligibility via Central Histopathology Review, patients may be consented for randomisation. Patient Information Sheet C and a complementary Patient Information DVD are provided to facilitate this process. Patient Information Sheet C explains the aim, trial arms, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator or delegate should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time, without compromising their care. The patient should be given ample time (a minimum of 24 hours) to read Patient Information Sheet C and view the Patient Information DVD and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

Please note that the content of the Patient Information DVD can also be viewed using the website address:

www.birmingham.ac.uk/loris, which is provided in all Patient Information Sheets.

Eligible patients who decline randomisation will be asked to indicate the reason for this and this will be recorded on the Patient Screening/Enrolment Log. During the Feasibility Study only, eligible patients who have been supplied with the Patient Information Sheet C and access to the Patient Information DVD but decline randomisation, will be provided with an Accept/Decline questionnaire and an Expression of Interest Form for completion at home. This will be documented on the Patient Screening/Enrolment Log. The patient will then return the completed Accept/Decline questionnaires and Expression of Interest Form to SHORE-C, in the pre-addressed envelopes provided. This will complete the patient's study participation.

If the patient expresses an interest in participating in the trial (registration or randomisation), they should be supplied with the appropriate copy of the Informed Consent Form (A, B or C) and asked to sign and date the latest version. The Investigator or delegate must then sign and date the form. The patient's Trial Number (TNO) should be entered on the Informed Consent Form. A copy of the Informed Consent Form should be given to the patient and a copy should be filed in the hospital notes. The original copy should be placed in the Investigator Site File (ISF). A copy of Informed Consent Form C should also be sent to the Trial Office. Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial, the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner.

Electronic copies of the Patient Information Leaflet, Patient Information Sheets and Informed Consent Forms are available from the Trial Office and should be printed or photocopied onto the headed paper of the local institution. Copies of the Patient Information DVD will initially be provided during the site initiation process, further copies to be supplied upon request.

The patients' General Practitioner (GP) should be informed that they are taking part (randomised patients only) in the trial. A trial-specific GP Letter is provided electronically for this purpose and this should be accompanied by a copy of the patients signed Informed Consent Form C.

6 TRIAL ENTRY

Entering a patient into the LORIS trial is a two-stage process, with registration followed by randomisation. The steps in this process are described below.

6.1 Registration

6.1.1 Timeframe for Registration

Patients should be registered into the trial within 90 days of the initial diagnosis of DCIS being made.

6.1.2 Registering a Patient

Written informed consent must be obtained prior to registration and must be recorded on the appropriate Informed Consent Form (A or B). Patient registration will be performed via completion of both the Eligibility Checklist and the Registration Form followed by a telephone call to the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham.

The name of the Investigator directly responsible for the patient's care will be requested. Investigators must be registered with the LORIS Trial Office before they are permitted to register patients into the trial (see Section 14.1 Site Set-up and Initiation).

The following information must be provided:

- Name of site and responsible Investigator
- Patient's initials
- Date of birth

To register a patient, please telephone

☎ 0800 371 969 or ☎ 0121 414 7844

(Monday to Friday, 9.00 am to 5.00 pm)

Registration will be performed electronically. The patient will be assigned a unique TNO that will be used to identify the patient and should be recorded on the CRF and on any further correspondence with the LORIS Trial Office. At the end of the registration process, the site research team will:

- Ensure that the patient's TNO is added to the Informed Consent Form before taking 2 photocopies (original to be kept in the ISF, 1 copy in hospital notes, 1 copy to the patient)
- Inform the patient of the planned timelines for submitting the histology slides for Central Histopathology Review and for the subsequent outcome of the review to be available
- Add the patients details to the Patient Screening/Enrolment Log

The LORIS Trial Office will fax confirmation of trial registration to the main contact for the site research team.

6.1.3 Submitting Slides for Central Histopathology Review

All diagnostic histology slides should be submitted for Central Histopathology Review as soon as possible following patient registration, in accordance with the LORIS Pathology and Sample Collection Guidelines.

All diagnostic slides (including all levels) from ALL diagnostic biopsies performed (small volume core biopsy, VACB and open diagnostic surgical biopsy if applicable), to include H&E stained sections plus sections from any other biomarkers such as ER Immunohistochemistry (if performed) must be sent for Central Histopathology Review. The Central Histopathology Reviewers will review all diagnostic material examined by the reporting pathologist.

All slides should be labelled to include only the patient's TNO, sample histology number and the type of stain used. A copy of the anonymised histopathology report should be included with the slides, this should be

anonymised to contain only the patient's unique LORIS TNO, along with a completed Central Histopathology Review Request Form.

The histology slides should be sent to the Trial Office in a plastic slide carrier within the Safeboxes™ provided (to ensure additional protection of the slides) prior to review by the Central Histopathology Review team and delivery to the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham. Once at the HBRC, the histology slides will be digitally scanned and uploaded for secure online viewing by the Central Histology Review team.

The outcome of the Central Histology Review will be made available to sites within 7 days of receipt of the histopathology slides. Note that histology slides which are dispatched on Friday will not be received by the Trials Unit until Monday.

The histology slides will be returned to the reporting pathologist at the site.

6.1.4 Central Histopathology Review Process

The slides will be digitally scanned by the HBRC and made available for secure review by the trial's team of pathologists. The trial pathologists will base their assessment on the following criteria:

In the event that the slide scanner used by the HBRC is not operational, alternative arrangements will be made to ensure continuation of the Central Histopathology Review process. Sites will be informed of any potential delays in providing the outcome of the Central Histopathology Review. The diagnostic biopsy slides will either be:

- Couriered directly to each Central Histopathology Reviewer in turn or
- Scanned by one of the Central Histopathology Reviewers at their Hospital, to enable the images can be made available for digital review by the other central review pathologists

In both cases, the slides will be returned to the LORIS Trial Office for scanning at the HBRC, once the scanning machine is in operation again and then returned to the referring hospital

Eligible

- Lesions which are of low cytonuclear grade, or in the lower half of the intermediate grade category, and where low grade has been considered in the diagnostic categorisation
- No comedo-type necrosis
- No more than occasional mitoses - no more than 1 per 3 duct cross section
- Nuclei to show minimal pleomorphism and must not be more than 2.5 red blood cells in diameter

Ineligible

- Where differential for classification lies between intermediate and high grade disease
- Presence of comedo-type necrosis
- Frequent mitoses
- Nuclei more than 2.5 red blood cells in diameter
- Section quality does not permit confident assessment of these criteria

Each case will be reviewed by a minimum of two reviewing pathologists.

Patients will not be eligible for randomisation if the Central Histopathology Review reports invasive disease, high grade DCIS or intermediate to high grade DCIS. Patients will be eligible for randomisation if the review team deems the patients to have low or low to intermediate grade DCIS or disease that is lower down the spectrum such as ADH. This is to ensure the trial addresses current clinical practice. The central pathology review is acting only as a safety mechanism to ensure higher grade disease is not randomised

The outcome of the Central Histopathology Review (eligible or ineligible) will be notified via email to the main contact, the individual who registered the patient, the nominated lead pathologist and the Principal Investigator. It is suggested that patients are informed that reporting of DCIS spectrum is not a black and

white process and that central reporting is not overriding local reporting. It is a means of ensuring uniformity at this stage of this first trial of active monitoring.

The outcome of the Central Histopathology Review should be documented on the Patient Screening/Enrolment Log.

6.1.5 Patient Recruitment

Patients will be informed of the outcome of the Central Histopathology Review by the site research team at the earliest opportunity. Eligible patients will be invited to take part in the trial and will be provided with Patient Information Sheet C and access to the Patient Information DVD (see Section 5.5 Informed Consent), if the patient has not already had the opportunity to view the DVD.

During the Feasibility Study only, all patients who have been presented with Patient Information Sheet C and the Patient Information DVD but subsequently decline randomisation will be provided with an Accept/Decline questionnaire and an Expression of Interest Form for completion at home, if they should wish to do so. The site research team should first ensure that patients TNO is added to each form before these are provided to the patient. The purpose of the Expression of Interest Form is for patients to indicate if they would be happy to be contacted for telephone interview by the SHORE-C team (see Section 8.2 Patient Telephone Interviews) regarding their decision to decline the trial.

6.2 Randomisation

6.2.1 Timeframe for Randomisation

Patients who are deemed to be eligible for the study following Central Histopathology Review should be consented for trial entry as soon as possible.

Advice from the Cancer Waiting Times (CWT) Team regarding trial participation and CWTs states that a patient should not be denied the opportunity to participate in a trial purely in order to avoid a breach. If a patient breaches a 31/62 CWT target as a result of necessary steps, such as additional screening tests, introduced by the trial protocol, this will indeed register as a breach. However, since the patient will have been fully informed of (and consented to) the delay, this is acceptable.

6.2.2 Randomisation

Registered patients should be randomised into the trial upon completion of written Informed Consent Form C.

Following consent, patients will be asked by a member of the site research team to complete the baseline QoL questionnaires (having first completed the Accept/Decline questionnaire) *prior* to randomisation. The person administering the questionnaires should ensure that all questions and all pages of each questionnaire have been completed, and that the patient's TNO is added to each form.

Randomisation will be performed via completion of the Randomisation Form followed by a telephone call to the CRCTU at the University of Birmingham.

To randomise a patient, please telephone

☎ 0800 371 969 or ☎ 0121 414 7844

(Monday to Friday, 9.00 am to 5.00 pm)

The caller will be asked to confirm the patient's details as collected at registration are correct and confirm patient eligibility. The following patient information must also be provided:

- Forename
- Surname
- Hospital number
- NHS or Community Health Index (CHI) number

Patients will be randomised 1:1 using a computerised minimisation technique. Stratification variables include:

- Age: *<55, 55-65, >65*
- Detection method: *screen detected, symptomatic/incidental*
- Overall maximum diameter of microcalcification: *<2cms, 2-5cms, >5cms*
- Surgical intent: *breast conserving surgery, mastectomy*
- Intent to prescribe anti-oestrogen therapy: *no, yes*

Patients will be allocated either to Surgery or to Active Monitoring. On completion of the randomisation process, the caller will be immediately notified of the randomised allocation. The site research team will then:

- Ensure that the patient's TNO is added to the Informed Consent Form before taking 4 photocopies (original to be kept in the ISF, 1 copy in hospital notes, 1 copy to the patient, 1 copy to be sent to the Trial Office, 1 copy to the GP)

- Inform the patient of their randomised allocation without delay
- Forward the completed Accept/Decline questionnaire and completed baseline QoL questionnaires to SHORE-C, in the prepaid addressed envelope provided
- Complete the Patient Reported Outcomes Form with the patients contact details and send this to SHORE-C in the pre-paid addressed envelope provided (note that the Trial Office should not be provided with the patient's address or telephone number)
- Update the Patient Screening/Enrolment Log
- Add the patients details to the Patient Identification Log
- Forward the GP Letter and a copy of the completed Informed Consent Form C to the patient's GP

The LORIS Trial Office will fax confirmation of trial entry to the main contact and will also send the responsible clinician confirmation of the patient's entry into the trial by post.

During the Feasibility Study only, consenting patients may be contacted shortly after randomisation by the SHORE-C team for a telephone interview (see Section 8.2 Patient Telephone Interviews) regarding their decision to join the trial.

7 SCHEDULE OF EVENTS

Please refer to the Schedule of Events table in the introductory pages.

7.1 Surgery Arm Patients

7.1.1 Baseline

Baseline data will be collected, to include details of all the diagnostic biopsy histology, details of current or planned endocrine therapy, data on any current Hormone Replacement Therapy (HRT), Non-steroidal anti-inflammatory drugs (NSAIDs) and biguanides.

7.1.2 Treatment

7.1.2.1 Surgery

Patients randomised to the Surgery Arm should undergo appropriate surgery according to local guidelines. It is expected that patients will undergo surgery within 60 days of randomisation.

Data on all related surgical procedures will be collected on the CRF, this also includes data on immediate or delayed breast reconstruction.

7.1.2.2 Endocrine Therapy

The use of endocrine therapy is not mandated within the trial and should be used according to local protocol; however, data on the use of endocrine therapy will be captured on the CRF.

7.1.2.3 Radiotherapy

The need for post-surgical radiotherapy should be decided following surgery and prescribed according to agreed local protocols. The use of post-surgical radiotherapy is not mandated within the trial however; data on the use of radiotherapy will be collected on the CRF.

7.1.3 Annual Follow-up

It is expected that local protocols will mean that patients in the Surgery arm are seen in clinic annually, within one month of attending for annual mammography. In cases where it is not local protocol to see patients annually post-diagnosis, arrangements should be made to contact the patient by telephone, following the outcome of their mammogram. Any planned additional follow-up for patients in the Surgery Arm will be in accordance with local guidelines.

Annual follow-up data should be obtained from the clinical visit with the patient (where local policy allows) or from an annual telephone call to the patient. Patients should be contacted within 1 month of attending for their annual mammogram or following completion of any investigations, if indicated.

7.1.3.1 Mammography

Patients must be invited to attend for annual mammography for 10 years. After 10 years, follow-up will be according to local guidelines; for the majority of patients this will be within the NHSBSP or within a compatible follow-up trial (see Section 7.4 Concurrent Studies).

Following annual mammography, patients should be informed of the outcome of the mammogram as soon as possible, ideally within 2 weeks of mammography being carried out. Participating sites which inform patients of the outcome of their mammography via letter, should do so using one of two site-specific result letters; Recall or Non-recall. The result letters will be generated by the site, however, the Non-recall letter must contain appropriate wording regarding the recall interval (i.e. one year interval rather than three years). The appropriate result letter should be sent to the patient and a copy of the letter should be sent to the patient's GP, unless systems are in place to allow the GP to access the outcome of the mammogram independently. A copy of the letter should also be filed in the patients' medical notes. and it is anticipated that a copy of the letter will also be filed in the patients' medical notes.

If a patient fails to attend for a mammogram appointment, a second appointment should be sent. If the patient fails to attend the second appointment, the patient's GP should be contacted to ensure that the patients address is correct. If the address is correct, a letter should be sent to the patient and their GP by the site research team, asking them to contact their research nurse. If a patient does not respond to this invitation, the patient should be contacted by telephone. The site research team must make every effort to

ensure that patient contact details are up to date and that all changes of address occurring in the 5 years post-randomisation are notified to SHORE-C by completing the Change of Contact Details Form. Note that changes to patient address and telephone details will be maintained by SHORE-C only and should not be provided to the Trial Office. Changes to the patient's name should be notified to the Trial Office, by telephone only.

7.1.3.2 Breast Screening Programme Invitation

Patients should be advised to contact the Research Team at their randomising hospital if they receive an invitation to attend for a mammogram through the NHS Breast Screening Programme during trial participation. Patients do not need to attend these additional appointments.

7.1.4 Investigations and Treatment of Ipsilateral Breast Disease

Investigations and treatment of ipsilateral breast disease in the Surgery arm patients will be in accordance with local protocol.

7.1.5 Investigations and Treatment of Contralateral Breast Disease

Suspected new disease in the contralateral breast should be investigated and treated according to local protocol. Details of confirmed disease in the contralateral breast will be collected on the CRF.

7.1.6 Data Capture

Data on the outcome of annual mammography, all related investigations (regardless of outcome) and treatment, related referrals to other healthcare practitioners and development of new breast disease will be collected annually on the CRF.

Further details on the progression of disease, development of new breast disease and development of first related distant metastases will be reported on the appropriate CRF.

7.1.7 Related Adverse Event Review

Protocol-related AEs will be collected annually on the CRF from years 1-5. Any persisting, protocol-related adverse effects will be reported annually on the CRF from years 6-10. Serious Adverse Events (SAEs) will be reported from study entry until 5 years post-randomisation in accordance with Section 16 Adverse Event Reporting.

7.1.8 Survival

Sites should report patient deaths by completing the Death Form immediately upon being made aware of the event.

7.2 Active Monitoring Arm Patients

7.2.1 Baseline

Baseline data will be collected, to include details of all the diagnostic biopsy histology, details of current or planned endocrine therapy and data on any current Hormone Replacement Therapy (HRT), Non-steroidal anti-inflammatory drugs (NSAIDs) and biguanides.

7.2.2 Treatment

7.2.2.1 Surgery

Patients in the Active Monitoring arm will not undergo primary surgery.

7.2.2.2 Endocrine Therapy

The use of endocrine therapy is not mandated within the trial, however, data on the use of endocrine therapy will be captured on the CRF.

7.2.3 Annual Follow-up

Annual follow-up data will be obtained from an annual telephone call to the patient, until 10 years post-randomisation. Patients should be contacted within one month of attending for annual mammography or following completion of any investigations, if indicated.

Any planned additional follow-up for patients in the Active Monitoring arm will be in accordance with local guidelines.

7.2.3.1 Mammography

Patients must be invited to attend for annual mammography for 10 years. After 10 years, mammographic follow-up will be according to local guidelines; for the majority of patients this will be within the NHSBSP or within a compatible follow-up trial (see Section 7.4 Concurrent Studies).

Following annual mammography, patients should be informed of the outcome of the mammogram as soon as possible, ideally within 2 weeks of mammography being carried out. Participating sites which inform patients of the outcome of their mammography via letter, should do so using one of two site-specific result letters; Recall or Non-recall. The result letters will be generated by the site but must contain appropriate wording regarding the screening interval (i.e. one year rather than three years) and in the case of the Non-recall letter, the wording of the result of the mammogram must be carefully worded to ensure that this is conveyed to patients in a consistent and appropriate manor. The appropriate result letter should be sent to the patient and a copy of the letter should be sent to the patient's GP, unless systems are in place to allow the GP to access the outcome of the mammogram independently. It is anticipated that a copy of the letter will also be filed in the patients' medical notes.

If a patient fails to attend for a mammogram appointment, a second appointment should be sent. If the patient fails to attend the second appointment, the patient's GP should be contacted to ensure that the patients address is correct. If the address is correct, a letter will be sent to the patient and GP asking them to contact their research nurse. If a patient does not respond to this invitation, the patient should be contacted by telephone. The site research team must make every effort to ensure that patient contact details are up to date and that all changes of address occurring in the 5 years post-randomisation are notified to SHORE-C by completing the Change of Contact Details Form. Note that changes to patient address and telephone details will be maintained by SHORE-C only and should not be provided to the Trial Office.

7.2.3.2 Breast Screening Programme Invitation

Patients should be advised to contact the Research Team at their randomising hospital if they receive an invitation to attend for a mammogram through the NHS Breast Screening Programme. Patients do not need to attend for these additional appointments and should be advised not to.

7.2.3.3 Ipsilateral Mammographic Indications for Patient Recall

An increase in the number, or size, of the microcalcification in the index lesion should not prompt routine patient recall. Neither should changes in the appearances/morphology, as casting type microcalcification is known to become more prevalent with increasing size.

Mammographic changes that would warrant a recall to clinic for further investigations are:

- A new cluster of microcalcification which is not definitively benign, outwith the index lesion/quadrant or remote from the index lesion
- A new cluster of microcalcification, which is not definitively benign in the contralateral breast
- A new non-calcified lesion which is not definitively benign in either breast
- Developing asymmetry or mass around the index calcification

7.2.4 Radiological Second Opinion Service

When a radiological second opinion is required, the current images and any prior images (if not previously captured) will be locally anonymised and uploaded for review via Image Exchange Portal or the local equivalent, to enable the images to be reviewed via an NHS computer. Participating sites which are unable to transfer images in this way should submit anonymised images for review on CD via post, including the patient's TNO, date of birth and date of mammogram only as identifiers. A request for the radiology second opinion service should be emailed to the Trial Office.

The outcome of the radiology review will be notified via email to the main contact, reporting radiologist, nominated lead radiologist and Principal Investigator within 7 days of the images being uploaded.

7.2.5 Investigations and Treatment of Ipsilateral Breast Disease

Please see Flowchart 2: Investigation Algorithm, later in this section.

Investigational biopsies will be taken in the Active Monitoring arm patients, as deemed appropriate by the site research team. In the case of suspected new disease in the ipsilateral breast, the histology slides will be submitted to the Trial Office for Central Histopathology Review (as for the diagnostic slides pre-study entry), in accordance with the LORIS Pathology and Sample Collection Guidelines.

The outcome of the Central Histopathology Review will be reported as either continue Active Monitoring or discontinue Active Monitoring. If there is no change in DCIS morphology, or the patient is confirmed to have additional low risk DCIS or benign disease, the patient will continue with Active Monitoring. If DCIS other than low risk or if invasive disease is confirmed, the patient will discontinue Active Monitoring and should be treated according to local protocol.

The outcome of the Central Histopathology Review will be notified via email to the main contact, reporting pathologist and nominated lead pathologist within 7 days of the slides being received by the Trial Office.

Details of all investigations (regardless of outcome) and subsequent treatment will be collected on the CRF.

7.2.6 Investigations and Treatment of Contralateral Breast Disease

Suspected new disease in the contralateral breast should be investigated and treated according to local protocol. Details on confirmed disease in the contralateral breast will be collected.

7.2.7 Data Capture

Data on the outcome of annual mammography, related referrals to other healthcare practitioners, all related investigations (regardless of outcome), disease progression or development of new breast disease and related treatment will be collected on the CRF.

Further details on progression of disease beyond that of the entry criteria, development of new breast disease and development of first related distant metastases will be reported on the appropriate CRF.

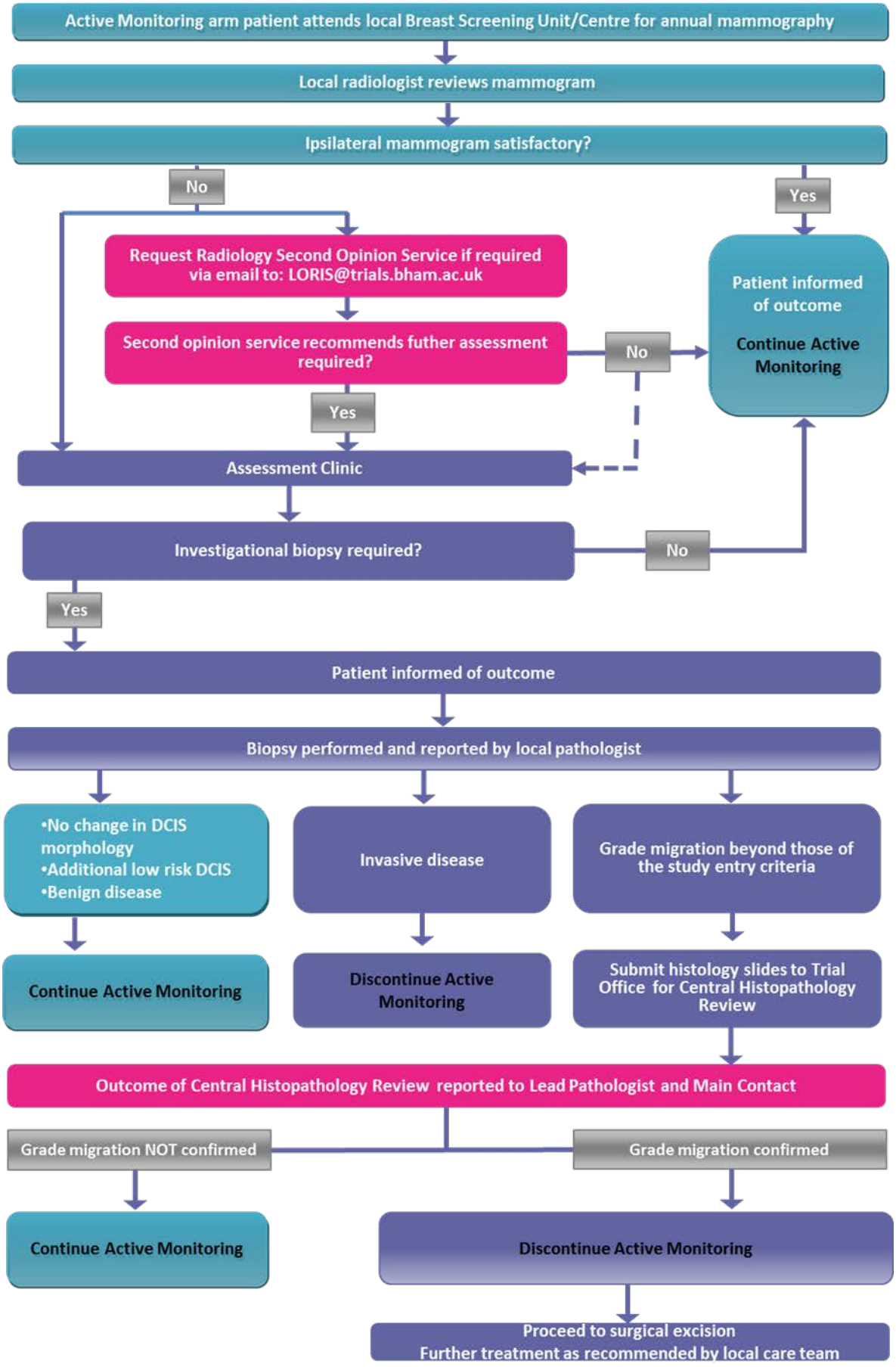
7.2.8 Related Adverse Event Review

Protocol-related AEs will be collected annually on the CRF from years 1-5. Any persisting, protocol-related adverse effects will be reported annually on the CRF from years 6-10. SAEs will be reported from study entry until 5 years-post randomisation in accordance with Section 16 Adverse Event Reporting.

7.2.9 Survival

Sites should report patient deaths by completing the Death Form immediately upon being made aware of the event.

7.2.10 Flowchart 2: Investigation Algorithm



7.3 Protocol Deviations and Patient Withdrawal

7.3.1 Protocol Deviations

The details of the protocol deviation (date, reason and type of deviation) should be clearly documented in the source data. A Deviation Form should be completed to notify the LORIS Trial Office of the deviation.

Patients will continue to be followed-up on an intent-to-treat basis.

7.3.2 Withdrawal of Consent

Patients may withdraw consent at any time during the trial. For the purposes of this trial, three different types of withdrawal are defined:

- The patient would like to withdraw from the randomised allocation, but is willing to be followed up according with the schedule of assessments (i.e. the patient has agreed that data can be collected and used in the trial analysis)
- The patient would like to withdraw from the randomised allocation and does not wish to undergo study assessments in accordance with the schedule of events but is willing to be followed up at standard clinic visits (i.e. the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis)
- The patient would like to withdraw from the randomised allocation and is not willing to be followed-up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis)

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data. A Withdrawal of Consent Form should be completed to notify the LORIS Trial Office of the patient's withdrawal.

7.4 Concurrent Studies

Investigators wishing to enrol patients into another trial should contact the LORIS Trial Office in the first instance. The LORIS Trial Management Group (TMG) will consider the enrolment of LORIS patients into other trials that do not interfere with the analysis of the primary outcome or introduce bias. Examples include trials of imaging, supportive treatment and adjuvant radiotherapy.

8 QUALITY OF LIFE

8.1 Quality of Life

The primary QoL aspect of the trial examines the hypothesis that the psychological well-being of women in the Active Monitoring arm is non-inferior to that associated with standard surgical and adjuvant treatments. In addition, these QoL outcomes will inform future patients diagnosed with low risk DCIS when making decisions about their treatment options. Patients will be asked to complete questionnaires at different time points (see Table 1 Timeline of Quality of Life Questionnaires, later in this section) that will look at factors that may influence:

- Decision to join or reject the trial using the Accept/Decline questionnaire (Feasibility Study only)
- Psychological adjustment - anxiety trait and ways of coping. Using the Speilberger State-Trait Anxiety Inventory (STAI) and Brief ways of coping questionnaire (baseline only)

In addition, the impact that either Surgery or Active Monitoring may have on anxiety state and general well-being is measured using:-

- STAI
- SF-36v2 Health Survey

8.1.1 Accept/Decline Questionnaire

During the Feasibility Study, women who are offered participation in the trial will be invited to complete an Accept/Decline questionnaire. The questionnaire initially asks patients if they have agreed or not to trial entry. Patients then rate on a 5-point Likert scale to what extent they agree or disagree with a list of 19 reasons that might influence their decisions. This questionnaire has been employed in several research studies examining entry into randomised clinical trials (45) including the on-going PulMiCC (Pulmonary Metatastectomy in Colorectal Cancer) trial.

8.1.2 Brief COPE Questionnaire

The Brief Ways of Coping Questionnaire (46) assesses how individuals cope with stressful situations via problem-solving and emotion-regulation. Participants will indicate whether they “have been doing this a lot”, “doing this a medium amount”, “doing this a little”, “haven’t been doing this” in respect to 28 questions.

8.1.3 State-Trait Anxiety Inventory

The STAI consists of 2 questionnaires with 20 items, each rated on simple 4 point scales. It is a well-known, validated research clinical tool for evaluating anxiety proneness (Trait) and the current state of anxiety or anxiety change (State). It is self-administered and has been used successfully in many breast cancer studies.

8.1.4 SF-36v2 Health Survey

The SF-36v2 Health Survey is a 36-item instrument for measuring Health-Related QoL (HRQoL) in a general population via patient self-report. The SF-36v2 measures the following eight health concepts, which are relevant across age, disease, and treatment groups: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being).

8.1.5 Euro Qol EQ-5D (EQ-5D)

The EQ-5D is a health status measure comprised of 5 attributes or dimensions; mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The single summary scores derived from the EQ-5D will be used in QALY analyses and in cost-effectiveness and cost-utility analyses.

Table 1. Timeline for Quality of Life Questionnaires

	Time points (months)							
Questionnaire	**Baseline**	**3**	**6**	**12**	**24**	**36**	**48**	**60**
Accept/Decline (Feasibility Study only)	x							
Brief COPE	x							
STAI Trait Anxiety	x							
STAI State Anxiety	x	x	x	x	x	x	x	x
SF-36v2 Health Survey	x	x	x	x	x	x	x	x
EuroQol EQ-5D	x	x	x	x	x	x	x	x

With the exception of the baseline QoL questionnaires that are completed by the patient prior to randomisation, all other questionnaires will be distributed directly to the patients' home address by SHORE-C, for completion at the designated time points. A member of the SHORE-C team may contact the patient if the questionnaires that have not been returned or have not been completed fully.

The site research team should inform SHORE-C of any changes to the patients address or telephone number by completing the Change of Contact Details Form. Note that changes to patient address and telephone details will be maintained by SHORE-C only and should not be provided to the Trial Office.

8.2 Patient Telephone Interviews

During the Feasibility Study, a proportion of women (12-15) will take part in a telephone interview with a researcher from SHORE-C. These interviews will explore the usefulness of the trial information (Patient Information Sheet and Patient Information DVD) supplied, their thoughts on the LORIS study and which aspects of the study influenced their decision to participate or not. A small proportion of women may refuse their randomised allocation; it would be helpful to interview these women also. It is important that both women who accept or decline LORIS study entry are interviewed.

9 HEALTH ECONOMICS

9.1 Form of the Health Economic Evaluation

If Active Monitoring is found to be an effective approach in the treatment for confirmed low risk DCIS then it is likely that there will be important cost implications for the health care sector. For example, the patient will avoid initial standard surgery and adjuvant treatment (according to local protocol) and will instead be monitored by annual mammography and be treated as an outpatient, thus avoiding an inpatient stay and resources may be saved. However, active monitoring may, or may not, incur unexpected or unscheduled costs due to additional appointments for reassurance using health care resources for example in providing counselling between mammography screens. Therefore all associated resource use costs incurred by both approaches need to be assessed in conjunction with measures of effectiveness.

The aim of the economic evaluation is to determine the cost-effectiveness of active monitoring compared with surgery and adjuvant therapy for low risk DCIS. Although the trial has been designed as a non-inferiority trial, the most appropriate type of analysis is a cost-effectiveness analysis (47). Cost-effectiveness will be determined in two ways: a cost-effectiveness analysis will be undertaken based on a number of outcomes including the cost per additional surgical treatment avoided at 10 years and cost per diagnosis of ipsilateral breast cancer, utilising the clinical outcome data collected within the trial. In addition, a cost-utility analysis will be undertaken to calculate the cost per additional quality-adjusted life year (QALY) gained. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D questionnaire at the time points described in Section 11.1. In the first instance, the evaluation will consider costs incurred by the health service in the delivery of both treatment pathways. However, information on costs incurred by patients will also be collected in order that an evaluation from a wider societal perspective can also be undertaken.

9.2 Cost Data Collection

Data collection will be undertaken prospectively for all trial patients so that a stochastic cost analysis can be undertaken. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource uses to be monitored from the trial by the site research team (but not directly from the patients) include the following:

- Consultation time required to explain each procedure for explanation and consent
- Surgical procedures (identification of procedures will be collected as part of the trial data collection; resource use associated with procedures will be collected from time and motion study where appropriate or staff / expert opinion)
- Adjuvant therapy (which is provided according to local protocol and will differ across sites). This data will be captured by a survey of protocols from the range of sites and the full range will be tested in the probabilistic sensitivity analysis
- Resource use involved with mammography procedures (from a staff survey questionnaire or experts and/or (compared with) HRG cost data for mammography)
- Costs involved with other related procedures, including level of health care professional involvement in the procedure, equipment required, overheads, consumables and drugs including anaesthesia
- Any additional procedures required where initial treatment is unsuccessful or incomplete
- Duration of inpatient stay for the surgical procedure

Information on additional related primary or secondary care contacts will also be collected from women to ensure any resulting resource use from additional complications is recorded. The best approach to this data collection is likely to be the cross sectional approach to investigate community based healthcare and participant resource use for the first 5 years post randomisation and follows that used by the ProtecT Trial.

A Patient Costs Questionnaire is used to collect patient data, on private travel for hospital appointments and time off work for example, with the aim of obtaining cross-sectional community based healthcare and participant resource use for the first 5 years post randomisation. However, to achieve this, a specific resource use questionnaire is distributed to all women at one time point. In the Feasibility Study, the questionnaire will be distributed to women 2 years after the first woman is randomised. This approach will capture some women at 24 months post randomisation, some at 20, 19, 18 12, 6 months etc., for a number of different time points, depending when randomised. The approach can be used to ensure that no woman receives more than one questionnaire. The questionnaires will be designed to ask women about their resource use in the previous 4 months. In the main trial (24-60 months) questionnaires will again be administered to women at a single time point (excluding those who participated during the feasibility phase) and participants will be asked about resource use in the previous 6 months. The questionnaire will contain questions to determine out of pocket expenses incurred (e.g. transport costs) when attending for treatment and private time costs including time lost from work. This approach would capture specific resource use for all women randomised into the study for complete coverage of five years. This approach follows the success of capturing the analogous data for men in the NIHR-HTA funded ProtecT Trial and CAP studies currently in progress for prostate cancer. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each trial patient. Published sources for these costs will include Unit Costs of Health and Social Care (48) and NHS Reference costs. Also some primary cost data will be collected from a representative sample of participating hospitals.

Participants will be sent the Patient Costs Questionnaire by post directly to their home address by SHORE-C

10 MAMMOGRAPHIC IMAGE LIBRARY

The trial will generate a library of anonymised mammogram images. The aim of any future image studies would be to identify potential radiological features that might predict cases likely to progress or identify early signs of progression.

Sites will prospectively collect the raw image data that will be anonymised with the patients Trial Number (TNO) and transferred securely to Royal Surrey Hospital in accordance with the radiology manual.

The image library is maintained and managed by the NCCPM based at Royal Surrey County Hospital will undergo full and regular backup to a remote secure facility.

Participating sites which do not use Picture Archiving Computer Stores or an equivalent platform, should submit anonymised images for review on CD via post to the National Coordinating Centre for the Physics of Mammography (NCCPM) based at Royal Surrey County Hospital, including the patient's TNO, date of birth and date of mammogram only as identifiers.

11 SAMPLE COLLECTION

11.1 Tumour Paraffin Blocks

Paraffin embedded tumour blocks will be collected for translational research. Please be aware that it will be the responsibility of the local site research team to obtain their patient's pathology material if the material is stored at a separate site to the randomising hospital.

It is appreciated that in some instances there may insufficient diagnostic material available for research purposes. If the local pathology team are concerned that there is insufficient tissue available for research, this should be communicated to the LORIS Trial Office.

The site research team may request the return of tumour blocks collected as part of the trial at any time by submitting a request to the Trial Office.

11.1.1 Primary Diagnostic Core Biopsies

The patient's diagnostic paraffin embedded tumour block(s), (small volume core biopsy and Vacuum Assisted Core Biopsy (VACB) or Vacuum Assisted Core Biopsy (VACB) alone as first line diagnostic approach or small volume biopsy or VACB plus open diagnostic surgical biopsy (without clear margins) or open diagnostic surgical biopsy (without clear margins)) from study entry will be requested Samples should be sent to the Edinburgh Cancer Research Centre in accordance with the LORIS Pathology and Sample Collection Guidelines. Please note that if a patient had multiple biopsies performed, all biopsy tumour blocks will be requested.

A core will be removed from the diagnostic block and any remaining tissue will be returned to the local pathologist.

In cases where the patient had multiple biopsies, there is no requirement to send the tissue block of those samples that contained no DCIS.

11.1.2 Surgical Excisions

Sites will be requested to forward representative tumour blocks from the surgical resection specimens to Edinburgh Cancer Research Centre in accordance with the LORIS Pathology and Sample Collection Guidelines.

A copy of the associated pathology report will be requested for each patient, this should be anonymised to contain only the patient's unique LORIS TNO and returned to the Trial Office.

The blocks will be retained at the Edinburgh Cancer Research Centre for research purposes.

In cases where no DCIS was evident in the surgical sample, there is no requirement to send the surgical sample.

11.1.3 On-Study Diagnostic Biopsies

Sites are requested to forward representative tumour blocks from all future diagnostic blocks to Edinburgh Cancer Research Centre in accordance with the LORIS Pathology and Sample Collection Guidelines.

The blocks will be retained at the Edinburgh Cancer Research Centre for research purposes.

12 ADVERSE EVENT REPORTING

The collection and reporting of AEs will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AE are listed in Appendix 1. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

12.1 Reporting Requirements

12.1.1 Adverse Events

AEs (see Appendix 1 for definition) are commonly encountered in patients undergoing treatment for DCIS. The safety of these treatments is already well characterised, therefore only related AEs experienced as a direct result of the trial protocol will be reported.

12.1.2 Serious Adverse Events

Investigators should report related AEs that meet the definition of an SAE (see Appendix 1 for definition) and are not excluded from the reporting process as described below.

12.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisations for:
    - Protocol defined treatment, as this information is captured elsewhere on the CRF
    - Pre-planned elective procedures (including breast reconstruction, as this information is captured elsewhere on the CRF)
    - Treatment for progression of the patient's DCIS or breast cancer, as this information is captured elsewhere on the CRF
- Progression or death as a result of the patient's DCIS or breast cancer, as this information is captured elsewhere on the CRF

12.1.2.2 Expected Serious Adverse Events

We are not expecting any SAEs to occur as a result of participation in this study. The following are regarded as expected SAEs for the purpose of the study and should not be reported on an SAE Form, as this information will be captured elsewhere on the CRF:

- SAEs relating to radiotherapy
- SAEs relating to breast reconstruction
- SAEs relating to adjuvant treatment for breast primary cancer or recurrence
- Hematoma, wound infection or seroma, as a result of primary breast surgery

This is not an exclusive list and Investigators should only report SAEs which are attributable to the study protocol.

12.1.3 Reporting Period

Details of all related SAEs (except those listed in Section 12.1.2.1 and 12.1.2.2 above) will be documented and reported from study entry until 5 years-post randomisation. This extended reporting period should be sufficient for all harm associated with the trial protocol to be captured however, if a related SAE is identified after this period, the event should be reported to the Trial Office.

12.2 Reporting Procedure

12.2.1 Site

12.2.1.1 Adverse Events

Related AEs experienced from study entry until 5 years post-randomisation should be reported in the AE section of the CRF.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 2). Any related AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the CRF using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

12.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting, refer to the Serious Adverse Event Form Completion Guidelines contained in Section 5 of the ISF.

AEs defined as serious and which require reporting as an SAE (excluding events detailed in Section 12.1.2.1 and 12.1.2.2 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE, which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Principal Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trial Office using one of the numbers listed below, as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

🖷 0121 414 8392 or 🖷 0121 414 7989

On receipt, the Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet by the Trial Office, which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, please contact the Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trial Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trial Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

12.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

12.2.2 Trial Office

On receipt of an SAE Form, relatedness will be determined independently by a Clinical Coordinator. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an Unexpected and Related SAE.

12.2.3 Reporting to the Research Ethics Committee

12.2.3.1 Unexpected and Related Serious Adverse Events

The Trial Office will report all events categorised as Unexpected and Related SAEs to the Research Ethics Committee (REC) within 15 days.

12.2.3.2 Other safety issues identified during the course of the trial

The REC will be notified immediately if a significant safety issue is identified during the course of the trial.

12.2.4 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

12.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection

The Case Report Form (CRF) will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Eligibility Checklist	Confirmation of eligibility	As soon as possible after registration
Registration	Patient details; confirmation of local diagnosis of non-high grade DCIS	As soon as possible after registration
Randomisation	Patient contact details; details of stratification variables; intended surgery	As soon as possible after randomisation
Baseline	Details of biopsy histology (with copy of diagnostic biopsy report), concomitant medications (HRT, endocrine therapy (current/planned), NSAIDs)	Within 1 month of randomisation
Surgery	Details of type of surgery performed, pathology of the DCIS specimen and any invasive disease identified, adverse events	Thirty days following completion of planned surgery (ies)
Additional Treatment	Details of any radiotherapy, endocrine therapy, chemotherapy administered and adverse events	As soon as possible following any additional treatment performed or commenced
Additional Investigations	Details of any additional mammography, other imaging or other biopsies performed	As soon as possible following any additional imaging or biopsies.
Annual Follow-up	Survival, outcome of annual mammogram and record of related interventions and referrals, concomitant medications (HRT, endocrine therapy, NSAIDs), persisting protocol related adverse effects, health resource usage	Within 1 month of patient annual mammogram or as soon as possible following investigations or treatment if indicated
Withdrawal	Date of withdrawal, type of withdrawal	Immediately following patient's request
Subsequent DCIS Report	Date subsequent DCIS confirmed, side and site of cancer, diagnostic method	As soon as possible following confirmation of subsequent DCIS
Invasive Breast Cancer	Date invasive breast cancer confirmed, side and site of cancer, method of detection	As soon as possible following confirmation of invasive breast cancer
New (or non-breast cancer) or Metastatic Cancer	Date cancer confirmed, side and site of cancer, method of detection, details of biopsy (if applicable) and treatment details	As soon as possible following confirmation of new or metastatic cancer
Deviation	Date of deviation, type of deviation	Immediately upon discovering deviation
Death	Date of death, details of death	Immediately upon notification of patient's death

The CRF must be completed, signed and dated and returned to the Trial Office by the Investigator or an authorised member of the site research team (as delegated on the SS&DL) within the timeframe listed above. Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data. The exception to this would be QoL data and health economics data which will be recorded directly onto CRF and is therefore considered source data. Any discrepancies between the CRF and source data should be explained. If any information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Trial Office and a copy filed in the ISF.

Trial forms may be amended by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

13.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

14 QUALITY MANAGEMENT

The trial is being conducted under the auspices of the CRCTU according to the current guidelines for GCP. Participating sites will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki 1996 (Appendix 3).

14.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition, all participating Investigators will be asked to sign the necessary agreements and registration forms and supply a current CV to the Trial Office. All members of the site research team will also be required to sign the SS&DL which should be returned to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

14.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the LORIS Trial Quality Management Plan. Additional on-site monitoring visits may be triggered, for example, by poor CRF return, poor data quality, low SAE reporting rates, or an excessive number of patient withdrawals or deviations. If a monitoring visit is required, the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the LORIS Trial staff access to source documents as requested.

14.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms C for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the TMG and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC.

14.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trial Office of any inspections.

14.5 Notification of Serious Breaches

Sites are requested to notify the Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach where required and in undertaking any corrective and/or preventive action.

The conditions and principles of GCP in connection with that trial or;

The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree:

The safety or physical or mental integrity of the subjects of the trial; or

The scientific value of the trial

15 END OF TRIAL DEFINITION

For the purposes of REC approval, the end of trial date is deemed to be 6 months after the date of last data capture or the final analysis of predictive biomarkers, whichever is later. This will allow sufficient time for the completion of protocol procedures, data collection and data input.

The duration of time for which patient follow-up data will be collected is dependent on future funding arrangements. Current funding is secured for this to continue for 10 years after the start of the trial, and further funding will be sought for this to continue long term.

The LORIS Trial Office will notify the REC that the trial has ended and a summary of the clinical trial report will be submitted to the REC within 12 months of the end of trial.

16 STATISTICAL CONSIDERATIONS

The first part of the trial is a Feasibility Study, the aim of which is to demonstrate enough eligible patients can be identified and recruited over the course of the trial to robustly answer the main trial objectives. The patients randomised during the two-year Feasibility Study will form part of the total (932) patients to be recruited.

The success of the Feasibility Study will be determined by showing a sufficient number of patients can be randomised meeting a combination of outcomes that ensures the main trial can adequately recruit to target within the given timeframe.

16.1 Feasibility Study

16.1.1 Definition of Outcome Measures

See Section 2.1.2 Outcome Measures.

16.1.2 Analysis of Outcome Measures

The only objective of the Feasibility Study is to show that the number of patients identified to take part in the study that are subsequently shown to be eligible, are consented and then randomised is sufficient to enable the main trial to continue and recruit an adequate number in a timely manner to robustly answer the main trial objective. No formal statistical testing will take place during the feasibility phase. Descriptive statistics as outlined in Sections 16.1.3 and 16.1.4 will be calculated in order to monitor and determine if progression to the main trial is feasible. The specific progression criteria are detailed below in Section 16.1.5

16.1.3 Planned Interim Analyses

Assessment of the success of the feasibility phase will be made at the end of the second year of recruitment. This approach recognises that there is likely to be a learning curve for both individual sites and the trial as a whole and allows time for specific recruitment problems to be identified and addressed. The Trial Coordinator will maintain close contact with sites and gather feedback from sites regarding both problems and successes in relation to performance on the above outcome measures. The TMG will hold monthly teleconferences during the feasibility phase of the study to review the screening log information and completed Accept/Decline Questionnaires to determine what actions are required to address any recruitment issues. The DMC will convene after 12 months of opening to review the feasibility outcome measures at the half way stage.

16.1.4 Planned Final Analysis

Assessment of the progression criteria will take place at the end of the twenty-fourth month of the Feasibility Study. Success in the progression criteria would demonstrate how the main trial can achieve the targeted recruitment and robustly answer the main trial objectives as detailed below. If the progression criteria are met, the trial will proceed, and will initiate at least 60 sites and will recruit for an additional 4 years to achieve the target of 932 patients.

16.1.5 Specific Progression Criteria from Feasibility Study to Main Trial

- 20 sites trained, open and recruiting by the end of year 2
- 60 patients randomised by the end of year 2
- Mean monthly recruitment of at least 6 patients in the last 4 months, as defined above

16.2 Main Trial

16.2.1 Definition of Outcome Measures

See Section 2.2.2 Outcome Measure of Main Trial.

16.2.2 Analysis of Outcome Measures

The primary research question to be addressed by this analysis asks if active monitoring for newly diagnosed, asymptomatic, low grade DCIS is non-inferior in terms of ipsilateral invasive breast cancer survival time when compared to surgical intervention to remove all traces of DCIS at diagnosis.

The primary aim is to test the null hypothesis that active monitoring of women diagnosed with low risk DCIS is not non-inferior in terms of invasive breast cancer free survival time compared to treatment with surgery. Invasive breast cancer survival time will be compared across the two arms on a per protocol and intent-to-treat basis, using a 1-sided (5% significance level) log-rank test for non-inferiority and a hazard ratio with a one-sided 95% confidence interval.

There is very little relevant evidence of the actual ipsilateral invasive breast cancer rate amongst low risk DCIS patients and an event rate of 2.5% at 5 years reflects current evidence (26). A difference in invasive breast cancer survival of no more than 2.5% is judged as clinically acceptable both by the TMG and the wider breast cancer clinical community. This gives a non-inferiority margin for the trial defined as an absolute reduction in the 5 year ipsilateral invasive breast cancer free survival rate at 5 years of 2.5% i.e. from 97.5% to 95% and this equates to a hazard ratio of HR=2.02 . Models for survival data will be considered to take into account the stratification factors and other potentially important prognostic factors.

All analyses will be carried out for both per protocol and intent to treat study populations. The primary and secondary outcomes will be calculated for all patients and compared between treatment groups. Time to event outcomes will be calculated for all patients and methods described by Kaplan and Meier used to present survival curves. The log-rank statistic will be used to test hypotheses.

Results from the Brief COPE will allow us to dichotomise women into two groups, those who manage a situation using a problem focused approach and those who have a detached method of coping.

The STAI permits us to measure changes in state anxiety over time. We will examine changes using Analysis of Covariance (ANCOVA) with baseline trait and state anxiety as covariates.

The SF-36v2 measures overall health related QoL by examining changes in the 8 health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) from baseline over time. Data will show how QoL is affected within and between the two groups (Surgery and Active Monitoring) over a 5 year period.

Health economic data will be used to provide a cost-effectiveness and cost-utility analysis and sensitivity analysis will be performed. The first stage of the economic analysis will be conducted at the end of the Feasibility Study. A second and final stage of analysis will be undertaken towards the end of the trial, using the data analyses from the trial, when 75% of the patients have reached 5 years follow-up. At the last stage there will be two components to the analysis: a within trial analysis and a model-based analysis. The evaluation of the Feasibility Study (after 2 years) will be a model based analysis only. The purpose of this is to ensure all relevant data for conducting the full economic evaluation are being appropriately identified and collected.

Model-based analysis will be carried out at the end of the Feasibility Study and again when 75% of patients have reached 5 years follow-up.

A decision analytic model will be used to allow the extrapolation of cost and effectiveness parameters beyond the data observed in a clinical trial (and to allow extrapolation to other settings). The model will, therefore, consider treatment over total disease duration and will include surgical treatments provided in the longer term. An individual sampling model (such as a Markov model) or similar model will be used to ensure time to event can be analysed. The model-based analysis will initially be conducted at Stage 1 and draw upon follow-up data up to 24 months (feasibility phase) and also make use of published data and assumptions to predict costs and benefits into the long-term. The analysis will then be repeated at Stage 2, using the longer follow-up data, but still predicting costs and effects beyond the trial end.

Results of all economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalizability of the results.

16.2.3 Planned Sub Group Analyses

Treatment efficacy will be investigated descriptively for subgroups of patients included as stratification factors: age, overall maximum diameter of microcalcification, surgical intent, detection method and intent to prescribe anti-oestrogen therapy.

16.2.4 Planned Interim Analysis

The primary and secondary outcomes will be analysed descriptively and presented to an independent DMC annually, along with information relating to trial recruitment and conduct, data completeness, treatment compliance and safety (see Section 17.6 Data Monitoring Committee).

16.2.5 Planned Final Analyses

The study will complete recruitment within 6 years and the analysis will take place when all patients have been followed-up for at least 5 years. Patients will continue with mammographic follow-up for a minimum of a further 5 and additional analysis will be undertaken.

16.2.6 Sample Size Justification

The sample size calculation is based on the primary outcome of ipsilateral invasive breast cancer survival time. The primary analysis will be a comparison of the ipsilateral invasive breast cancer free rate between the Active Monitoring arm and Surgery Arm using a log-rank test for non-inferiority. The justification for the sample size is explained below.

Taking into account all published 5 year recurrence rates post-surgery for low risk disease, excluding contralateral disease and ipsilateral *in situ* disease, the projected recurrence rate (ipsilateral invasive breast cancer rate) at 5 years in the Surgery Arm is 2.5%. There is no relevant published data on 5 year ipsilateral invasive cancer rate in non-operated asymptomatic mammogram-detected low risk DCIS diagnosed by VACB and centrally reviewed. We have therefore based our non-inferiority calculation on extrapolation from the surgical data, estimates of overtreatment and what is judged to be a clinically relevant non-inferiority margin.

The non-inferiority design aims to show that not treating low risk DCIS with surgery is no worse (than a given margin) than treating with surgery. The primary outcome is ipsilateral invasive breast cancer free survival time and we will use a log-rank test for non-inferiority to determine whether no surgery is as good as surgery in these low risk DCIS patients by comparing the survival distributions of the two treatment groups. Because of the directional nature of the hypothesis, this non-inferiority test is one-sided. Jung *et al.* (49) derived an asymptotically exact sample size formula for the non-inferiority log-rank test to give the number of patients required to reject the null hypothesis that no surgery is worse than surgery, based on a given level of power and significance, assuming exponential survival distributions for both treatment groups, uniform patient accrual during a specified accrual period and set number of events during a period of follow-up, uniform censoring and no loss to follow-up.

The one-sided Type I error rate is set at 5% and Type II error rate set at 20%, giving 80% power. The accrual period will be over 6 years and patients will be in follow-up for 5 years. The ipsilateral invasive breast cancer free rate at 5 years, based upon previous data (see above), is estimated to be 97.5%. The non-inferiority margin of maximal difference is determined to be 2.5%, therefore if the invasive breast cancer free rate at 5 years in the untreated group is not worse than 95%, then non-inferiority would be concluded since it falls within 2.5% of the treated population's invasive breast cancer free survival rate (97.5%). This decision was reached by the TMG, which comprises clinicians and patient representatives as well as statisticians. This non-inferiority margin equates to a hazard ratio of 2.02

The sample size calculation, given the above information estimates that 50 events will be sufficient to answer robustly the primary research question and it is estimated that 932 patients are required to achieve this number of events allowing for a 10% loss to follow-up/non-adherence rate.

17 TRIAL ORGANISATIONAL STRUCTURE

17.1 Sponsor

The trial is sponsored by the University of Birmingham.

17.2 Coordinating Centre

The trial is being conducted under the auspices of the CRCTU, University of Birmingham according to their local procedures.

17.3 Quality of Life Coordinating Centre

The QoL data collection will be coordinated by SHORE- C.

17.4 Trial Management Group

The Chief Investigator, Co-investigators including the Trial Statistician, trial Radiologists, trial Pathologists, Quality of Life team, Trial Manager and Trial Coordinator will form the TMG. The TMG will be responsible for the day-to-day conduct of the trial. They will be responsible for the clinical set-up, promotion, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications. The TMG will hold regular meetings (usually by teleconference). During the Feasibility Study, the TMG will hold monthly teleconferences.

17.5 Trial Steering Committee

The independent Trial Steering Committee (TSC) has been set up to oversee the trial. Membership will be composed of TMG members, representatives from the funders and at least one patient advocate. The TSC will meet shortly before commencement of the trial and annually (usually by teleconference), they will supervise the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the trial.

17.6 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC is scheduled to meet one year after the trial opens to recruitment and then annually until 5 years after the last patient is recruited.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC who will convey the findings of the DMC to the TMG, funder and sponsor. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. Specific progression criteria from the feasibility phase to the main trial are outlined in Section 16.1.5.

17.7 Finance

This is an investigator-initiated and investigator-led trial funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme.

The Sponsor will pay Research Costs, as defined in the Clinical Site Agreement, to participating sites.

The trial has been adopted by the NIHR Cancer Research Network Portfolio.

18 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html) (see Appendix 3).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998, Human Tissue Act 2008, Human Tissue (Scotland) Act 2006 and Good Clinical Practice (GCP). The protocol will be submitted to and approved by the Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trial Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

19 CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. With the patient's consent, their full name, date of birth, National Health Service (NHS) number, or in Scotland the Community Health Index (CHI), address, postcode, hospital number will be collected at trial entry to allow QoL questionnaires to be sent to patients' home address and to facilitate tracing through the Cancer Registries and the Health and Social Care Information Service (service formally provided by the Office of National Statistics) and to assist with long-term follow-up via other health care professionals e.g. patient's GP. Patients will be identified using only their unique TNO, initials and date of birth on the CRF and correspondence between the Trial Office and the participating site. However, patients are asked to give permission for the Trial Office to be sent a copy of their signed Informed Consent Form C, which will not be anonymised. This will be used to perform in-house monitoring of the consent process and will also be forwarded the patient's GP and possibly other health care professionals involved in the treatment of the patients.

The Investigator must maintain documents not for submission to the Trial Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trial Office will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party other than the central radiology and pathology review team and those directly involved in the care of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries, laboratory staff). Representatives of the LORIS Trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

20 INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm.

21 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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23 APPENDIX 1 – DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial, which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Related Event

An event which resulted from the administration of any of the research procedures.

Serious Adverse Event

An untoward occurrence that:

- Results in death unrelated to the original DCIS diagnosis
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus, hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

24 APPENDIX 2 – COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

The full NCI CTCAE document is available on the NCI website, the following address was correct when this version of the protocol was approved:

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

25 APPENDIX 3 – WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

7. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

8. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

9. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

10. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

26 NOTES

LORIS Trial Office

Cancer Research UK Clinical Trials Unit
University of Birmingham
Edgbaston
Birmingham, B15 2TT

☎ 0121 414 3017 ☎ 0121 414 3057

🖷 0121 414 8392

✉ LORIS@trials.bham.ac.uk

Registration and Randomisation

☎ 0800 371 969 or ☎ 0121 414 7844
Monday to Friday 9.00 am to 5.00 pm

Serious Adverse Event Reporting

🖷 0121 414 8392 or 🖷 0121 414 7989

@CRCTU Cancer Research UK Clinical Trials Unit