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

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Quality of Life Coordinating Centre

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Translational Coordinating Centre

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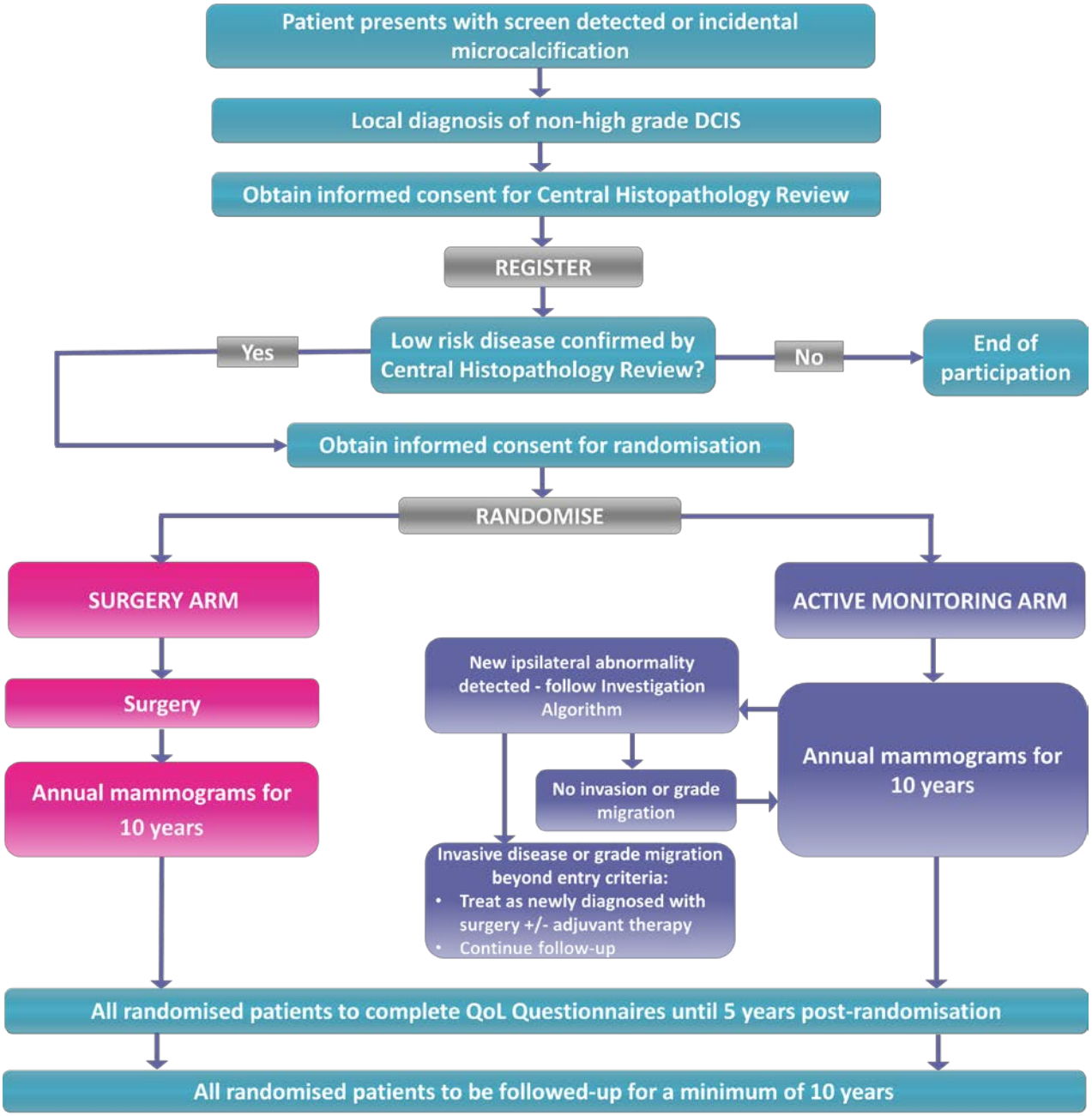
Trial Schema



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.