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The LORIS Trial: A multicentre, randomised phase III trial of standard surgery versus active monitoring in women with newly diagnosed low risk ductal carcinoma *in situ*.

Chief Investigator Adele Francis

University of Birmingham UK

Prof MWR Reed (CoI)

University of Sheffield

United Kingdom Breast Cancer Screening Programme

Established 1988

Age 47 – 73 years

3 yearly 2 view digital mammography

UK NBSP

2011 – 2012	2.3 million women screened
	19,300 cancers (1:120)
	80% invasive
	20% non-invasive (DCIS)

UK NBSP

Breast conserving surgery	74% Non Invasive 78% Invasive
Mastectomy rate <15mm	11%
Immediate reconstruction for DCIS	44%
Survival at 10 years	90%

Public Health England

ABS
ASSOCIATION OF BREAST SURGERY

NHS Breast Screening Programme and Association of Breast Surgery

An Audit of Screen-Detected Breast Cancers for the Year of Screening April 2012 to March 2013

Case Study LM Age 66

Jan 2014	NBSP 20mm Stromal deformity
PMH	Pulmonary hypertension Multiple pulmonary emboli
FH	Mother locally advanced breast cancer
Medications	Warfarin
VAB	DCIS (intermediate grade) + radial scar and benign breast change large haematoma (Hb75g/L) + transfusion

Case Study LM

Extensive discussion of treatment options

Recommendation guidewire localised WLE + SNB

Patient choice – bilateral mastectomy! Woried about increased future risk and mothers experience and avoid radiotherapy

Surgery unilateral mastectomy

Uncomplicated recovery – no residual invasive or non-invasive disease

Case Study MB Age 66

Nov 2000 (Age 53) NBSP

Right 1cm unifocal IDC + DCIS

Left multi-focal DCIS

Advice: bilateral mastectomy with option of immediate reconstruction

Case Study MB

Patient “overwhelmed by diagnosis and treatment recommendation”

Patient choice (after considerable discussion):

Right wire localised WLE + SNB

15mm grade 2 IDC ER positive HER2 negative

1 node positive

Declined completion axillary clearance

Left breast DCIS – declined treatment

Case Study MB

Adjuvant radiotherapy to right breast

+ Tamoxifen

+ annual mammography

Case Study MB - Follow-up

2001	Left mammogram ↓ microCa^{++} and possible mass lesion Recommended repeat biopsy Patient declined
2006	Agreed to extend tamoxifen beyond five years
2008	Changed to anastrazole
2011	Stopped endocrine treatment
2013	Mammogram unchanged Discharged from follow up to NBSP

Daily Mail

Collect DOUBLE Mail Reward Points all this week

What's causing your sore throat?

Good Health

For every life saved by breast screening, 3 patients undergo unnecessary treatment

NEEDLESS CANCER THERAPY FOR 4,000 WOMEN

Twitter frenzy as BBC Emily 'dresses like Doctor Who baddie'

EXPRESS.co.uk

Home of the Daily and Sunday Express

Our Paper

Front and Back Pages, E-Edition and Back Issues...

HOME › NEWS / SHOWBIZ › UK NEWS

UK NEWS

NHS: 7,000 WOMEN IN CANCER 'BLUNDER'

Tuesday January 19,2010

By Daily Express Reporter

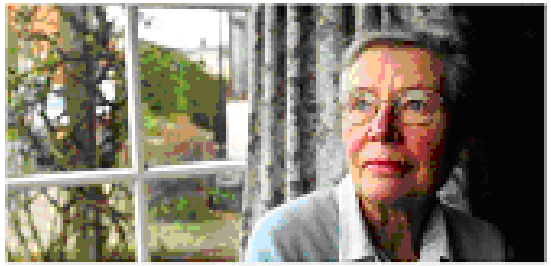
Have your say(2)

SEVEN thousand women are wrongly told they have breast cancer every year by the NHS screening programme, experts said last night.

A disturbing report claims that one in four diagnoses is incorrect, as lumps

7,000 women are wrongly told they have breast cancer every year by the NHS, experts said

Case study: 'I didn't know enough to decide'



Hazel Thornton describes the treatment process as "like a conveyor belt"

From The Times

January 19, 2010

'I'd already had this thing taken out before I found out my options'

Case study

Hazel Thornton was called in for breast screening 18 years ago and the diagnosis was ductal carcinoma in situ. "The doctor just said, 'This doesn't look normal. I think we better excise it, don't you?' I'd already had this thing taken out of me by the time I found out what the treatment options were," she said.

Mrs Thornton, from Rowhedge, Essex, was 57 when she had part of her breast removed. She now campaigns for informed consent and fuller disclosure of risks and benefits of screening.

"If I had known, I may have opted for 'watchful waiting' before I had surgery." She took tamoxifen for 17 months before stopping because of side-effects.

Hazel Thornton campaigns for fuller disclosure of the risks of

From The Sunday Times

April 19, 2009

Anger at 'needless' breast cancer ops

Women are calling for changes to the NHS screening system

Flanders said screening caused her considerable harm

Sarah-Kate Templeton

WOMEN have expressed their bitterness and hurt about undergoing breast surgery after research showed that 10 patients will be treated unnecessarily for every life saved.

There are now calls for changes in the national breast screening programme to allow suspect cancers to be monitored instead of using surgery in the first instance.

The change would bring the treatment of breast cancer more into

European Journal of Cancer
Volume 39, Issue 12 , Pages 1746-1754, August 2003

Quantifying the potential problem of overdiagnosis of ductal carcinoma *in situ* in breast cancer screening

M.-F. Yen, L. Tabár, B. Vitak, R.A. Smith, H.-H. Chen, S.W. Duffy

Received 7 October 2002; received in revised form 9 January 2003; accepted 4 February 2003.

Abstract

Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England

Stephen W Duffy, Laszlo Tabar, Anne Helene Olsen, Bedrich Vitak, Prue C Allgood, Tony H H Chen, Amy M F Yen and Robert A Smith

J Med Screen 2010;**17**:25–30
DOI: 10.1258/jms.2009.009094

See end of article for authors' affiliations

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Accepted for publication
2 December 2009

Objectives To estimate the absolute numbers of breast cancer deaths prevented and the absolute numbers of tumours overdiagnosed in mammographic screening for breast cancer at ages 50–69 years.

Setting The Swedish Two-County randomized trial of mammographic screening for breast cancer, and the UK Breast Screening Programme in England, ages 50–69 years.

Methods We estimated the absolute numbers of deaths avoided and additional cases diagnosed in the study group (active study population) of the Swedish Two-County Trial, by comparison with the control group (passive study population). We estimated the same quantities for the mortality and incidence rates in England (1974–2004 and 1974–2003, respectively). We used Poisson regression for statistical inference.

Results A substantial and significant reduction in breast cancer mortality was associated with screening in both the Two-County Trial ($P < 0.001$) and the screening programme in England ($P < 0.001$). The absolute benefits were estimated as 8.8 and 5.7 breast cancer deaths prevented per 1000 women screened for 20 years starting at age 50 from the Two-County Trial and screening programme in England, respectively. The corresponding estimated numbers of cases overdiagnosed per 1000 women screened for 20 years were, respectively, 4.3 and 2.3 per 1000.

Conclusions The benefit of mammographic screening in terms of lives saved is greater in absolute terms than the harm in terms of overdiagnosis. Between 2 and 2.5 lives are saved for every overdiagnosed case.

The University Of Sheffield.

Modern mammography screening and breast cancer mortality: population study

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EDITORIAL by Elmore and Harris

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STUDY QUESTION

Does inviting women to mammography screening in the context of a national screening programme reduce the risk of death from breast cancer?

SUMMARY ANSWER

Among women aged 50-69, biennial invitation to modern mammography screening was associated with a 28% reduction in deaths from breast cancer. In Norway, around 368 women would need to be invited to prevent one death from breast cancer during their lifetime.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

New trials on screening are unrealistic, and updated observational studies are needed to reliably compare the effects on breast cancer mortality among screened and unscreened women. Mammography screening is likely to provide a substantial benefit for breast cancer mortality, and careful ascertainment of exposure to screening is crucial in observational studies.

Participants and settings

All Norwegian women aged 50 to 79 years during 1986-2009. Within that period (1995-2005), a national mammography screening programme was gradually implemented, with biennial invitations sent to women aged 50 to 69 years.

Design, size, and duration

This dynamic cohort was prospectively followed-up, using individual information about date of invitation to screening, date of breast cancer diagnosis, and date of breast cancer death. We used multiple Poisson regression analysis to estimate breast cancer mortality rate ratios comparing women who were invited to screening (intention to screen) with those who were not invited, with a clear distinction between women with a diagnosis before (without potential for screening effect) and after (with potential for screening effect) a first invitation to screening. We took competing causes of death into account by censoring women from further follow-up who died from other causes. In the analysis, we adjusted for age, birth cohort, national trends in breast cancer mortality, and county of residence. Based on the observed reduction in mortality from breast cancer, combined with all cause and breast cancer specific mortality in Norway in 2009, we used the CISNET (Cancer Intervention and Surveillance Modeling Network) Stanford simulation model to estimate how many women need to be invited to biennial mammography screening in the age group 50-69 years to prevent one death from breast cancer during their lifetime.

Main results and the role of chance

During 15 193 034 person years of observation (1986-2009), deaths from breast cancer occurred in 1175 women with a diagnosis after being invited to screening and 8996 breast cancer deaths in women who had not been invited before diagnosis. After adjustment for age, birth cohort, county of residence, and national trends in deaths from breast cancer, the mortality rate ratio associated with being invited to mammography screening was 0.72 (95% confidence interval 0.64 to 0.79). To prevent one death from breast cancer during their lifetime, 368 (95% confidence interval 266 to 508) women would need to be invited to screening.

Bias, confounding, and other reasons for caution

The strengths of this study include the prospective design of a large cohort, and the use of an incidence based mortality approach with accurate distinction of women with a diagnosis of breast cancer before or after a first invitation to screening. None the less, we cannot rule out confounding by unmeasured factors related to the non-random introduction of screening by county.

Generalisability to other populations

These results are likely to be relevant to other population based mammography screening programmes.

Study funding/potential competing interests

This study was supported by the Norwegian Research Council as part of the official evaluation of the Norwegian mammography screening programme. We have no competing interests.

Mortality rate ratio of breast cancer among women aged 50-79 who were invited or not invited (reference) to the Norwegian mammography screening programme, 1986-2009

Screening status	Deaths from breast cancer	Person years*	Crude rate* (per 100 000)	Adjusted† mortality rate ratio (95% CI)
Not invited	8996	12 785 325	70.4	1.0 (reference)
Invited	1175	2 407 709	48.8	0.72 (0.64 to 0.79)

*Using incidence based mortality with separation of breast cancer cases (and corresponding person years at risk) diagnosed before and after invitation to the screening programme.
†Adjusted for age, birth cohort, national breast cancer mortality trends, and county of residence.

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- Research: Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial (*BMJ* 2014;348:g366)
- News: Screening has not reduced deaths from breast cancer, study shows (*BMJ* 2013;346:f3780)
- Research: Women's views on overdiagnosis in breast cancer screening: a qualitative study (*BMJ* 2013;346:f158)
- Views & reviews: Harms from breast cancer screening outweigh benefits if death caused by treatment is included (*BMJ* 2013;346:f385)

TOO MUCH MEDICINE

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While the benefits are small, the harms of screening are real and include overdiagnosis, psychological stress, and exorbitant healthcare costs

The harms and benefits of modern screening mammography

Women need more balanced information

Joann G Elmore professor of medicine, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA jelmore@u.washington.edu
Russell P Harris professor of medicine, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

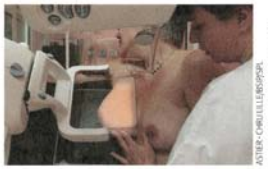
The Swiss Medical Board noted that the current debate on the benefits and harms of mammography screening is based on outdated randomised controlled trials (RCTs) and that it was "non-obvious" that the benefits outweighed the harms.[1] They recommended that no new mammography screening programmes should be introduced in Switzerland and that the existing ones should be phased out.[1]

The board relied on a review by another panel: the Independent United Kingdom Panel on Breast Cancer Screening.[2] Using data from the published RCTs, the UK panel estimated that for every 10 000 women aged 50 invited to screen for the next 20 years, about 43 would avoid a death from breast cancer and the remaining 9957 would receive no mortality benefit. About 129 women would be treated unnecessarily as a result of overdiagnosis, a ratio of three women with overdiagnosed cancers to one woman with a breast cancer death avoided.

As both panels noted, data from older RCTs are not ideal for determining the benefits and harms of modern day screening. Instead, observational studies such as in the linked paper will be increasingly relied on to monitor changes over time.[3]

Much has changed since women were first enrolled into the breast cancer screening RCTs, one of which started 50 years ago. These include factors that influence the incidence of breast cancer and the timing of diagnosis. Most importantly, breast cancer treatment has noticeably improved, and this may partially explain some of the benefit attributed to mammography.

Recent findings from the 25 year follow-up of the Canadian National Breast Screening Study underscore uncertainties about the applicability of the older RCTs to current screening policies. That study showed no benefit from screening, perhaps partly due to participants receiving more effective treatment than in the older RCTs.[4] Some commentators have asked for new trials, but results would take decades and it would still be questioned whether further changes in risk factors, treatment, and technology had made the RCT results obsolete.



ASTIER - CHRISTOPHE LEBROCQUIN

Party girl

The new cohort study from Norway[5] adds important information to a growing body of observational evidence estimating the benefits and harms of screening. The authors followed women for more than two decades during a time when the country's breast cancer screening programme was gradually implemented. They found that, for every 10 000 women screened, about 27 deaths from breast cancer might be avoided.

Although observational studies may provide more up to date estimates than the old RCTs, they also come with considerable uncertainty. As these studies compare groups in different periods (before and after screening programmes begin) or in different geographical areas (with and without screening programmes), they are susceptible to selection bias.[3] It is not surprising that observational studies in Norway and other Scandinavian countries have disagreed about the estimated mortality benefit of screening mammography.[6-9] The benefit reported in the present study falls near the middle of these other published estimates.

Overall, evidence from both observational studies and RCTs indicates a benefit from screening mammography. Interestingly, the estimates from the observational studies do not differ greatly from those of the older RCTs: for every 10 000 women screened over 20 years, an estimated 27 versus 43 women, respectively, would avoid a breast cancer death. The Norwegian study largely confirms what is already known: the benefits of screening mammography are modest at best. While the benefits are small, the harms of screening are real and include overdiagnosis, psychological stress, and exorbitant healthcare costs.

So how can women be helped to make informed decisions about screening? Unfortunately they are rarely presented with balanced information. While the results of complex, imperfect science do not easily translate into memorable slogans, campaigns to promote mammography do often catch women's attention. Many individuals and groups actively promote mammography screening. Doctors discussing mammography with patients are more likely to mention the potential benefits than harms of screening.[10] One US hospital promotes monthly "mingle and mammograms" parties, with women being pampered before screening to calm their nerves.[11] These parties include appetizers, foot massages, and bags emblazoned with the logo "fight like a girl." In addition to appetizers, we suggest serving women balanced information about the benefits and harms of screening to chew on.

Knowledge gap

Concern about the amount and type of information on screening mammography made available to women is increasing internationally. In the United Kingdom, concerns about women receiving inadequate information when participating in their national screening programme led to the formation of a special "citizen's jury" of women to review the issue.[12 13] After hearing evidence from experts, one participant remarked: "I can't believe how much I didn't know."[14]

Beyond its relevance to women's decision making today, the Norwegian study should make us reflect on how to monitor the changing benefits and harms of screening. Future studies will hopefully allow analyses to account for changes over time in risk factors, screening technology, and treatment. Just as quality criteria have been defined for RCTs, creative study methods and quality metrics must be developed for observational studies evaluating large screening programmes.

For future independent boards to be able to conclude that the breast cancer screening decision has finally become obvious, careful assessment of ongoing screening programmes will be required. In the meantime, make yourself comfortable—this may take a while.

Competing interests and references are on bmj.com.
Provenance and peer review: Commissioned; not externally peer reviewed.
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NEWS, p 4; RESEARCH, p 14

January 2010

Who evaluates public health programmes? A review of the NHS Breast Screening Programme

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If 2000 women are screened regularly for 10 years, one will benefit from the screening, as she will avoid dying from breast cancer.

At the same time, 10 healthy women will, as a consequence, become cancer patients and will be treated unnecessarily.

THE LANCET

The Lancet, Volume 380, Issue 9855, Pages 1778 - 1786, 17 November 2012
doi:10.1016/S0140-6736(12)61611-0 Cite or Link Using DOI

Published Online: 30 October 2012

< Previous Article | Next Article

The benefits and harms of breast cancer screening: an independent review

Independent UK Panel on Breast Cancer Screening‡

Mounting controversy over whether women were getting the full picture led to a major review into the NHS screening programme by the internationally recognised public health expert Professor Sir Michael Marmot.

The review concluded screening saves around 1,300 lives each year, but leads to 4,000 women having treatment for cancer they never needed.

In the historic trials

- 1 life saved
- 3 diagnosed and treated without benefit

- The panel's review of overdiagnosis leads to their support for further research into DCIS, in particular:

- Current mammographic screening techniques now detect many more cases of DCIS than in the trials. The appropriate treatment of these is uncertain, because there is limited information on their natural history.

- The panel supports studies to elucidate the appropriate treatment of screen-detected DCIS.

LORIS

The Low Risk DCIS Trial

NIHR Health Technology Assessment programme

NHS National Institute for Health Research

Cancer Research UK Clinical Trials Unit @CRCTU

Patient Representation

Maggie Wilcox

Health Economics

Prof Tracy Roberts

PROMs

Prof Lesley Fallowfield

Dr Valerie Jenkins

Radiology

Prof Andrew Evans

Dr Matthew Wallis

Pathology

Prof Andrew Hanby

Prof Sarah Pinder

Dr Jeremy Thomas

Translational Research

Prof John Bartlett

Statistics

Prof Lucinda Billingham

Miss Cassandra Brookes

Trial Management

Miss Claire Gaunt

Research Question

Can patients with newly diagnosed low risk Ductal Carcinoma in situ (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?

LORIS

Low or Intermediate Grade DCIS on Vacuum Biopsy

Pathology Central review confirms low risk criteria

Randomise

Active monitoring

Surgery

Key Aspects

- 2 year Pilot Phase
- Central pathology review
- Radiology second opinion service
- Patient Reported Outcomes QoL
- Health resource utilisation
- Translational research biobank

Key Eligibility Criteria

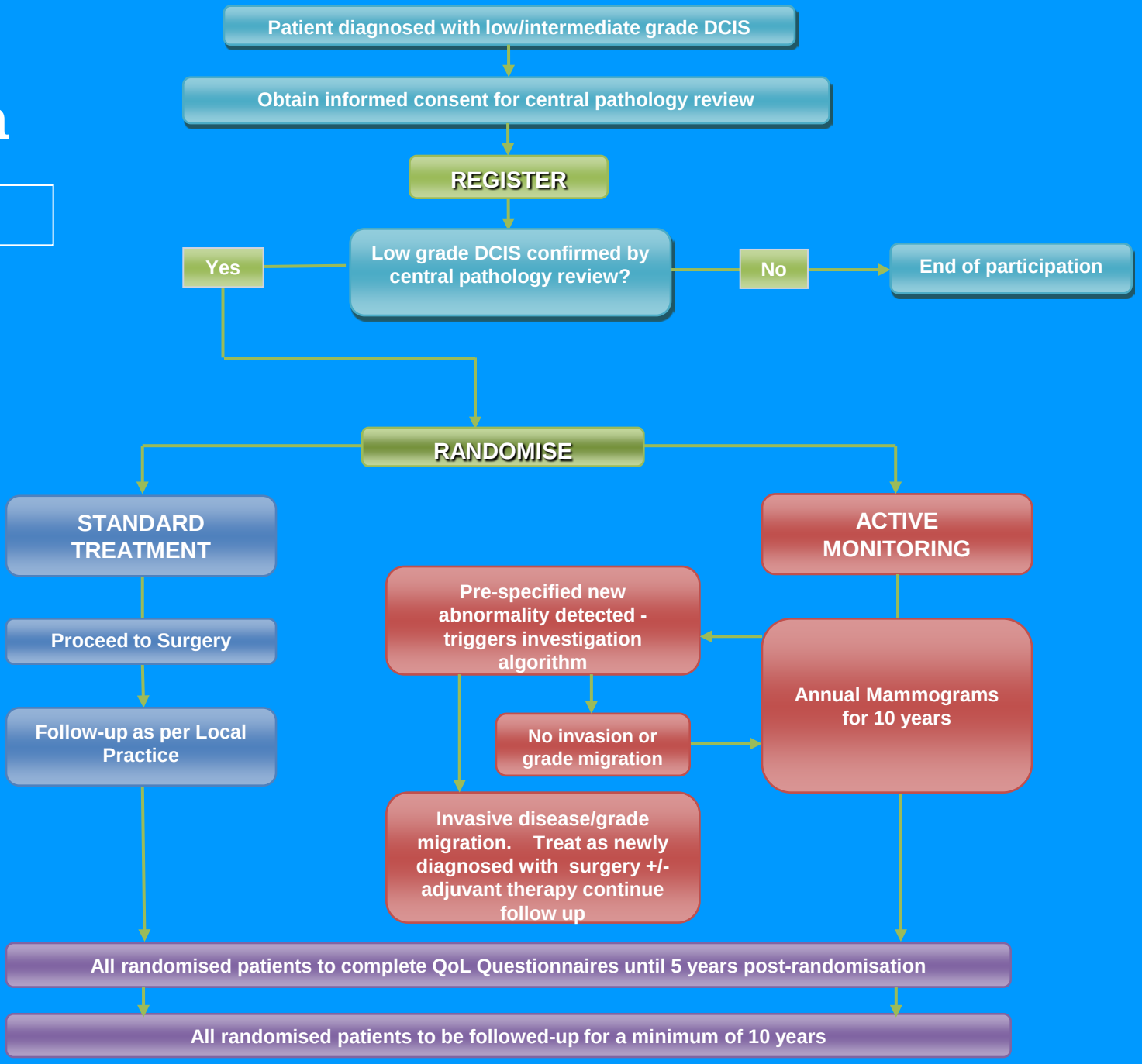
- Female, age ≥ 46 years
- Screen-detected or incidental microcalcification
- Low risk DCIS on large volume VAB, confirmed by central pathology review
- Patient fit to undergo surgery
- No previous breast cancer or DCIS diagnosis

Key Exclusion Criteria

- A mass lesion clinically, on ultrasound scan or mammogram at the site of the microcalcification before biopsy
- Previous invasive breast cancer or DCIS.
- High-risk group for developing breast cancer (as defined by NICE guidelines, or prior exposure to mantle radiotherapy)

Trial Schema

932 patients



Trial End Points

- Diagnosis of invasive breast cancer in the same breast
- Patient reported outcomes

- Overall survival
- Translational predictors of progression to invasive disease
- Time to surgery/mastectomy/mastectomy rate
- Health Economics

@CRCTU

Translational/Biomarker Summary

- *Tissue to be banked at diagnosis, resection and recurrence.*

Patient Pathway

Diagnostic VAB

- VAB 11G biopsy is a pre-requisite for trial entry, the number of 11G samples required depends on the size of the area of radiological abnormality but in a majority of patients a minimum of 6 cores is recommended.

- Microcalcification should be present on specimen radiography and a marker clip inserted at the time of VAB.
- USS visible marker clips are recommended.
- NHSBSP Assessment Guidelines for sampling should be followed

Diagnosis of Low or Intermediate Grade DCIS

- Discussed in MDT Meeting
- Patient given another trial information document and permission requested for sending Bx for central review.
- Patient registered for Trial.

CENTRAL PATHOLOGY REVIEW

- Grading of DCIS by pathologists is well recognised to be inconsistent, as shown in the NHSBSP pathology EQA scheme.

- All locally diagnosed low and intermediate grade biopsies will be centrally reviewed with a one week turn around time.

- Provides enhanced consistency of diagnosis prior to randomisation

Randomisation

Surgery +/- adjuvant RT and endocrine therapy OR

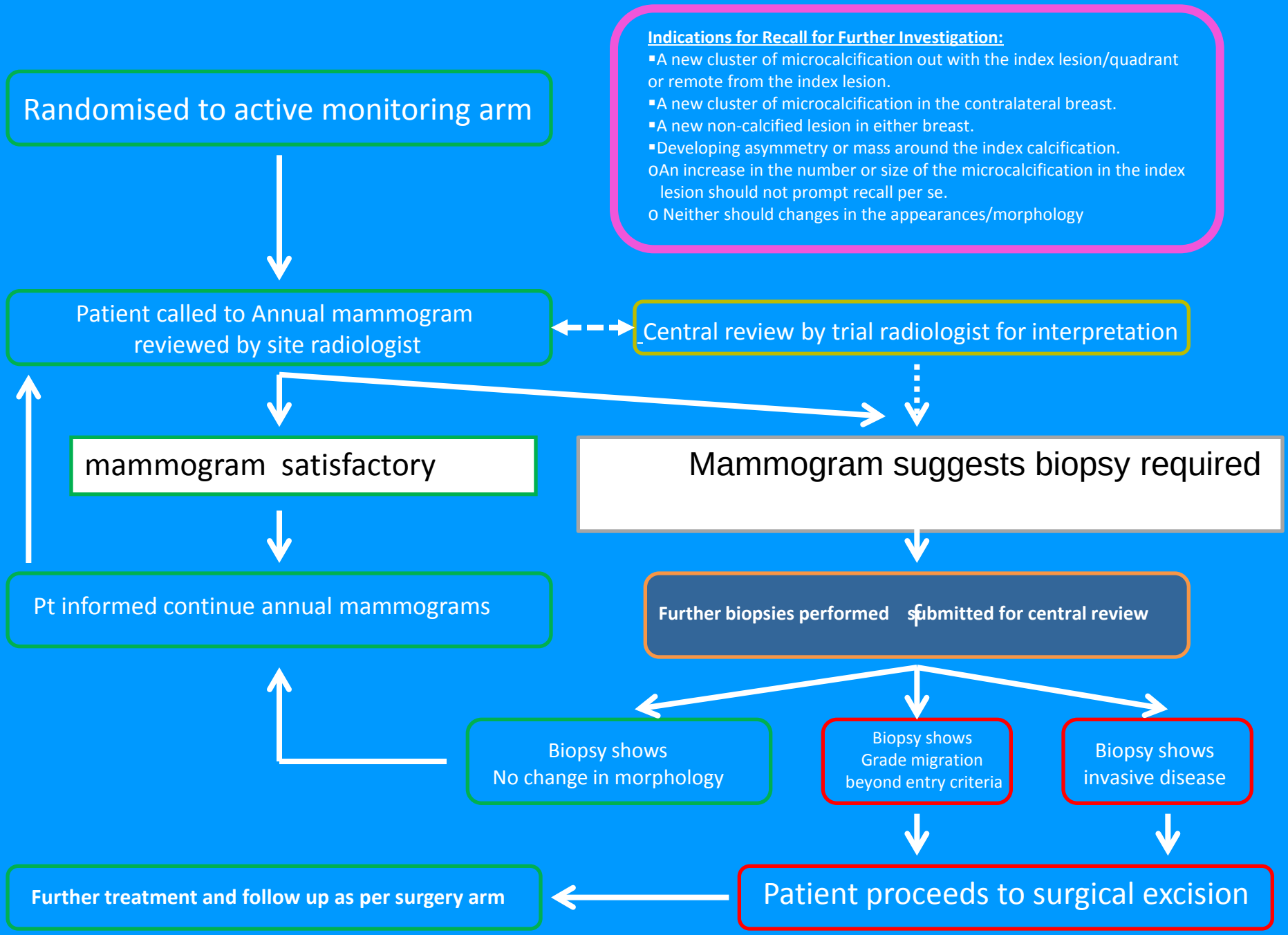
Active Monitoring

- Indications for recall for further investigation:
- ☐ 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.

- NOT indications for Recall
- An increase in the number or size of the microcalcification in the index lesion should not prompt recall.

- Neither should changes in the appearances/morphology, as casting type microcalcification is known to become more prevalent with increasing size.

- An expert radiological advice/second opinion service will be provided by the trial radiologists through image exchange platform for patients in the active monitoring arm if requested by the site. This advice will be provided within 1 week.


Indications for Recall for Further Investigation:
▪A new cluster of microcalcification out with the index lesion/quadrant or remote from the index lesion.
▪A new cluster of microcalcification in the contralateral breast.
▪A new non-calcified lesion in either breast.
▪Developing asymmetry or mass around the index calcification.
oAn increase in the number or size of the microcalcification in the index lesion should not prompt recall per se.
o Neither should changes in the appearances/morphology
Randomised to active monitoring arm
Patient called to Annual mammogram reviewed by site radiologist
Central review by trial radiologist for interpretation
mammogram satisfactory
Mammogram suggests biopsy required
Pt informed continue annual mammograms
Further biopsies performed submitted for central review
Biopsy shows No change in morphology
Biopsy shows Grade migration beyond entry criteria
Biopsy shows invasive disease
Patient proceeds to surgical excision
Further treatment and follow up as per surgery arm

The sample size calculation is based on the primary outcome of ipsilateral invasive breast cancer rate. 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 one-sided type I error is set at 5% and power is 80%. Assuming a 5 year ipsilateral invasive breast cancer free rate of 97.5% in the surgery arm, to exclude a difference of more than 2.5% at 5 years requires 932 patients.

The University Of Sheffield.

Conclusion

- LORIS offers the opportunity to address overdiagnosis and overtreatment of screen detected low risk DCIS.

- Recruitment will be the major challenge and lessons learnt from previous studies will be essential for success.