



Addressing overtreatment of screen detected DCIS; the LORIS trial



Adele Francis^{a,*}, Jeremy Thomas^b, Lesley Fallowfield^c, Matthew Wallis^d, John M.S. Bartlett^e, Cassandra Brookes^f, Tracy Roberts^g, Sarah Pirrie^f, Claire Gaunt^f, Jennie Young^f, Lucinda Billingham^f, David Dodwell^h, Andrew Hanbyⁱ, Sarah E. Pinder^j, Andrew Evans^k, Malcolm Reed^l, Valerie Jenkins^c, Lucy Matthews^c, Maggie Wilcox^m, Patricia Fairbrother^m, Sarah Bowden^f, Daniel Rea^f

^a Department of Breast Surgery, Nuffield House University Hospital Birmingham, Edgbaston, Birmingham, B15 2TH, UK

^b Western General Hospital, Edinburgh, UK

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

^d Cambridge Breast Unit, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK

^e Ontario Institute for Cancer Research, Toronto, Ontario M5G 0A3, Canada

^f Cancer Research UK Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT, UK

^g Health Economics Unit, University of Birmingham, Birmingham, B15 2TT, UK

^h St. James's Hospital, Leeds, UK

ⁱ Department of Histopathology, Academic Unit of Pathology, St James's University Hospital, Leeds, UK

^j Division of Cancer Studies, Department of Research Oncology, King's College London, UK

^k Ninewells Medical School, Dundee, DD1 9SY, UK

^l University of Sussex, Brighton, BN1 9PX, UK

^m Independent Cancer Patients Voices, London, EC1R 0LL

Received 18 December 2014; received in revised form 20 May 2015; accepted 16 July 2015

Available online 18 August 2015

KEYWORDS

DCIS

Low grade DCIS

Breast screening

Over treatment

Clinical trial

Breast cancer

Abstract Overdiagnosis, and thus overtreatment, are inevitable consequences of most screening programmes; identification of ways of minimising the impact of overdiagnosis demands new prospective research, in particular the need to separate clinically relevant lesions that require active treatment from those that can be safely left alone or monitored and only need treated if they change characteristics. Breast cancer screening has led to a large increase in ductal carcinoma in situ (DCIS) diagnoses. This is a widely heterogeneous disease and most DCIS detected through screening is of high cytonuclear grade and therefore likely to be important clinically. However, the historic practice of surgical treatment for all DCIS is unlikely to be optimal for lower risk patients. A clearer understanding of how to manage DCIS is required. This article describes the background and development of 'The low risk' DCIS trial (LORIS), a phase III trial of surgery versus active monitoring.

* Corresponding author. Tel.: +44 (0) 121 627 2000.

LORIS will determine if it is appropriate to manage women with screen detected or asymptomatic, low grade and intermediate grade DCIS with low grade features, by active monitoring rather than by surgical treatment.

© 2015 Elsevier Ltd. All rights reserved.

1. Background

A series of contradictory academic publications and protracted debate concerning the estimated benefits and harms of breast screening has attracted significant attention in the scientific and general press. An independent United Kingdom (UK) panel reviewed the evidence for harms and benefits of breast screening. The review team concluded that breast cancer screening does indeed save lives. However, from the available data, the team estimated that for each life saved by breast screening three women are overdiagnosed [1]. While limitations of the review and caveats to the interpretation and reliability of this headline metric are clearly stated, this review has provided many with reassurance that breast screening has an important role to play in reducing breast cancer mortality with an acceptable downside in terms of overtreatment. The Swiss medical board by contrast reviewing the same information reached the conclusion that there is ‘no clear evidence of any survival benefit’ but ‘clear evidence of overtreatment with up to 14 patients getting an unnecessary diagnosis for one who possibly benefits’ [2]. On this basis the board has recommended winding down the Swiss breast screening programme. These divergent interpretations are of course not new [3,4]. Consensus regarding how existing trial data should be interpreted seems as far away as ever. The contemporary relevance of data from screening trials conducted up to 30 years ago is also hard to define. Modern imaging and diagnostics result in more lesions being identified, investigated and treated than was the case in the era of the original screening trials. The magnitude of current overtreatment as a result of breast screening remains difficult to define accurately, leaving women of screening age and their doctors with a dilemma about the wisest course of action. Clinicians generally continue to recommend surgery in the absence of any available evidence-based strategy or access to an appropriate clinical trial. The UK screening review recommended research into the need for surgery for low grade ductal carcinoma in situ (DCIS), an approach regarded by the authors as appropriate to attempt to address overtreatment and avoiding the nihilism implied by discontinuation of screening altogether. A clinical trial is long overdue.

One striking and measurable consequence of breast screening has been a substantial rise in women diagnosed with DCIS. In the UK, the age standardised

incidence of DCIS has risen from 3.6/100,000 in 1988 to 16.2/100,000 [5], accounting for 20% of screen detected neoplastic lesions [6]. If all DCIS is destined to progress to invasive disease then it would be reasonable to assume that the treatment of screen detected DCIS would result in a reduction in the development of invasive breast cancer. However in the same period, i.e. 1988–2010, invasive breast cancer has risen from 90.9/100,000 into 126.2/100,000. [7] These data may be explained in part by improved detection techniques (including digital mammography and increased use of magnetic resonance imaging (MRI)), as well as by a true increase in invasive disease, due to epidemiological factors, but the natural history of ‘pure’ DCIS (that occurring in the absence of any invasive cancer) remains poorly understood.

Accepted criteria for the adoption of a screening test are that the natural history of the condition is understood and that treatment should be more effective if started early. It has long been assumed that early detection of DCIS and its immediate treatment will also result in health benefit, although there is no direct evidence for this. The trials demonstrating that adjuvant treatments do reduce recurrence of DCIS as further in situ or as invasive carcinoma have at the same time been unable to show an impact on mortality. DCIS is a heterogeneous disease with variable malignant potential and while there is no question that some DCIS will progress to invasive disease and indeed that high grade DCIS may harbour occult high grade invasive cancer [8], it is not fully understood which patients require urgent intervention and who can be safely left untreated. The Marmot review recommends that overtreatment be addressed by research [1]. At present DCIS is, somewhat crudely, segregated by grade. It is clear that high grade DCIS is associated with the development of high grade invasive carcinoma, is biologically more aggressive and that this is the grade most commonly detected by screening. Low and intermediate grade DCIS however account for approximately 30% of screen detected lesions and the certainty of progression to invasion is less clear. The remainder of this article describes the development of the low risk DCIS trial (LORIS), a prospective phase III trial of women with asymptomatic or screen detected low or low/intermediate grade DCIS randomised to immediate surgery and standard adjuvant treatment or to a non-interventional approach of active monitoring (see Fig. 1).

The Sloane Project is a UK wide, prospective audit of screen detected non-invasive cancer and atypical hyperplasia of the breast.

It is a multi-disciplinary project involving radiologists, pathologists, surgeons and oncologists.

The concentrated expertise of the Sloane Project steering group formed the core of the LORIS trial development group. From the outset, patient representatives from Independent Cancer Patients' Voice (ICPV) were included in this group. ICPV is a patient advocate group, independent of established UK cancer charities. Members of ICPV embraced the trial idea with enthusiasm and in many ways drove the protocol forward, steering it down a route acceptable to patients and clinicians alike. It was necessary for the trial protocol to address several specific areas and the key ones are considered individually below.

2. Eligibility

2.1. Age

There was agreement that the patients should be of screening age, from first invitation (between age 46 and 49) and that an upper age limit was not required. Women are not invited for screening in the UK after the age of 70 but may continue to attend on a three yearly basis by request (see [Table 1](#)).

2.2. Grade

This eligibility criterion is based both on the results of the UK DCIS 1 trial [9] which, from central review, showed comparable local recurrence with low and intermediate cytonuclear grade DCIS (hazard ratios (HR) 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 grades. If future pathological classification changes to describe high grade and non-high grade DCIS, based on more robust reproducible criteria rather than the currently more subjective low, intermediate and high grades, then the role of active monitoring in the entire non-high grade group could be considered. Wide discussion has provided consensus that inclusion in a trial with the randomization to active monitoring DCIS should be restricted to low grade disease, and intermediate grade with low grade features.

In order to address the recognised issue of reproducibility of cytonuclear grading of DCIS, real time central pathology review by expert DCIS pathologists using a bespoke web based system for slide review strives to ensure that high grade disease is excluded and that only patients with low grade, or intermediate grade with low grade features, are randomised into this trial. The

central pathology review provides internal consistency for meeting pathological entry criteria across all trial sites.

Until recently, the diagnosis of DCIS was made using small volume biopsies, i.e. 14 gauge (G), however large volume vacuum-assisted core biopsies (VACB) (e.g. 11G and 8G) are now considered the gold standard and are in widespread use in the UK. VACB provides a larger tissue sample and improves both the accuracy of classification of grade of DCIS and greater assurance of the absence of invasion [10,11].

2.3. Size

DCIS size eligibility criteria were a contentious issue during the protocol design. It was discussed at every opportunity during development with the wider breast cancer community. There were vociferous supporters of only small lesions being eligible and equal support for those who thought only patients requiring a mastectomy should be able to take part. The protocol writing group found no evidence that size should be an eligibility criterion. Individual clinicians may choose to only discuss the trial with patients who have DCIS of a size that they are comfortable with randomising, but a prospective randomised trial is the only way to address this issue.

There is no published trial of active monitoring of patients with low and low/intermediate grade DCIS of any size diagnosed with VACBs, subject to central pathology review and with no mass lesion clinically or on imaging. The lack of clear evidence of the benefit of surgery for this group of patients provides a strong rationale for offering the trial as an alternative approach for this condition.

3. Biopsy method

The trial pathology experts were united in their opinion that VACBs were required to determine eligibility and that small volume cores alone did not suffice and would not be sufficiently representative. Patients who proceed from small volume biopsies to VACBs have all diagnostic material reviewed.

4. Imaging criteria

Because the presence of a mass lesion on imaging is associated with of a higher chance of an invasive component at excision, those patients with any mass lesion present on radiological imaging or clinical examination were determined to be ineligible. The radiologists concluded, however, that breast ultrasound was not essential as a trial procedure but if performed as part of the standard diagnostic work up and a mass lesion was seen the patient was not eligible for trial entry; thus patients

are only eligible if they have screen detected or asymptomatic microcalcification with no evidence of a mass lesion.

5. Surgery arm

There was agreement that the surgery arm patients should receive the same treatment they would receive were they not in a trial, i.e. standard surgical and adjuvant treatment according to local protocol. There is great variation in local protocols both for definition of completeness of excision (i.e. regarding margin width of uninvolved tissue required), and application of adjuvant treatments for DCIS in the UK and standardisation of adjuvant treatment would not be practical [6].

6. Active monitoring arm

The protocol writing group was in agreement that in the active monitoring arm there should be no anti-oestrogen treatment because the question the trial addresses is that of overtreatment not undertreatment. There is no evidence to suggest how long patients treated by endocrine treatment alone should stay on therapy. To accommodate divergent opinion the trial will stratify for intended endocrine treatment.

Annual mammography was widely agreed to be an acceptable monitoring method, at least in the medium term. In the long term, however, follow up with alternative imaging modalities may supersede mammography. There was no enthusiasm for magnetic resonance imaging (MRI) to be part of the protocol at present, as there was a paucity of evidence for this and substantial evidence that it would lead to a higher unnecessary mastectomy rate.

7. Follow up in both arms

There are no data on the long-term outcome of patients receiving no treatment for VACB-detected low risk DCIS that has been subject to central pathology review. There are a few published series of patients in whom the initial pathological diagnosis was missed but on retrospective slide review were identified as having previously unrecognised DCIS. These patients therefore received no treatment. These women had a symptomatic presentation and did not have a VACB (i.e. would not have been eligible for LORIS for several reasons). Long-term outcome data from these series show that while a substantial number subsequently developed invasive tumours these occurred over a very long time-scale [12–15]. It was considered appropriate in this first trial of active monitoring to mandate at least 10 years of annual mammograms. Even longer follow-up is probably needed to produce data regarding the impact on

mortality and we have recognised the need to attract future funding for lifelong follow up in LORIS.

8. Recall and investigation

While spontaneous regression of DCIS has been proposed by some, it is assumed that the diagnosis of DCIs in these patients will persist long term and the object of follow up is to detect and treat subsequent invasive disease. An increase in the number, or size, of the microcalcification in the index lesion will not prompt routine patient recall, neither will changes in the appearances/morphology, as casting type microcalcification is known to become more prevalent with increasing size.

Mammographic changes that trigger protocol recall for further investigations are as follows:

- 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.

A second opinion service for participating radiologists is incorporated in the trial to promote a uniform approach in equivocal situations.

Recall in the surgical arm will be performed in line with standard practice.

9. Imaging tissue banks and translational research

Both the tissue samples and radiological imaging are being banked prospectively for future translational research. There have been multiple challenges that act as barriers to effective and high quality translational research in DCIS. These include some local variations in assessment of pathology, receipt of small samples, the requirement for fixation of all tissue for accurate 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, when linked to advances in current technology that allow the analysis of gene expression from very small quantities of DNA/RNA (100–200 ng) or from microdissected samples of as few as 100–1000 cells.

A widely recognised high priority breast cancer research question is to determine the factors in DCIS

lead to progression into invasive carcinoma [16]. There is limited information on the functional molecular events that drive progression of DCIS from the primary diagnosis of a pure in situ carcinoma to a frankly invasive lesion. It remains challenging to build a comprehensive picture of the events involved in progression of pure DCIS to invasive cancer with any certainty. Complex, branched models are proposed, with multiple mutational events driving multiple routes to invasive cancer [17–19], however recent data suggest that at least some fraction of pure DCIS may be molecularly distinct from DCIS which is identified associated with invasive cancer [20,21]. It may be that some DCIS may not develop the molecular alterations which lead to invasive cancer and therefore may represent a molecular state with low risk of progression.

While there are several potential diagnostic profiles available for risk stratification following a diagnosis of DCIS, existing candidate approaches, such as the

Genomic Health ‘DCIS Score’ [22] or the Kerlikowske triple positive IHC profile [23] have been unvalidated, until a recent report at San Antonio (2014) indicating a utility to the ‘DCIS Score’ [24]. The LORIS trial will prospectively collect diagnostic samples and immediate resection samples from those women undergoing surgery, as well as tissue samples from re-biopsy events and delayed surgical resections when these are required. This will form an annotated tissue sample collection to validate existing, and identify novel, molecular profiles associated with both indolence and progression to invasive disease.

An Imaging Data Repository is a further valuable resource in LORIS.

There is minimal information on how microcalcification, managed without surgery, changes over time and what, if any, signs precede progression to invasive disease. It is planned to prospectively bank all radiological images from the active monitoring arm.

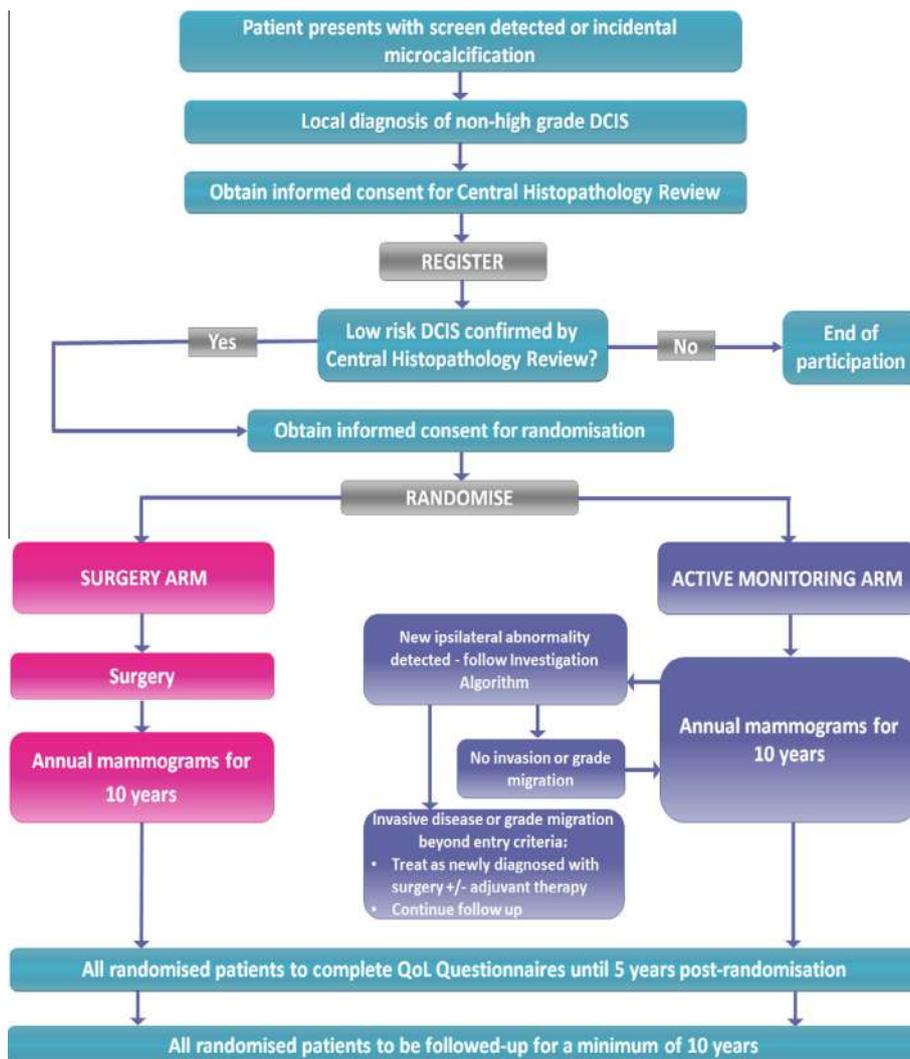


Fig. 1. Low risk DCIS (LORIS) trial flow diagram.

Table 1
Low risk DCIS (LORIS) trial key eligibility criteria.

<i>Inclusion criteria</i>
<ul style="list-style-type: none"> • Female, aged ≥ 46 years • Screen-detected or incidental microcalcification (unilateral or bilateral) • Histologically confirmed diagnosis of non-high grade ductal carcinoma in situ (DCIS) confirmed by local pathologist on either small volume core biopsy or, vacuum assisted core biopsy (VACB) or surgical biopsy • DCIS diagnosed ≤ 90 days before registration • Patient fit to undergo surgery and informed consent obtained
<i>Exclusion</i>
<ul style="list-style-type: none"> • Previous/current diagnosis of invasive cancer or ipsilateral DCIS • A mass lesion clinically or radiologically at the site of the microcalcification before biopsy • Any serious and/or unstable pre-existing condition that would prevent compliance with the trial or consent process • Recent onset ipsilateral blood-stained nipple discharge, unless cytology and/or ultrasound scan (USS) confirm concomitant duct ectasia • High risk group for developing breast cancer

10. Statistical design and end-points

As surgery is currently the standard of care, a non-inferiority design was considered most appropriate to answer the primary research question: is active monitoring non-inferior to surgery in terms of ipsilateral invasive breast cancer survival? The primary analysis will be a comparison of the ipsilateral invasive disease free survival time between the active monitoring and surgery arms using a log-rank test for non-inferiority on a per protocol and intent to treat population. The one-sided type I error is set at 5% and power is 80% and assumes a 5 year ipsilateral loco-regional disease free survival rate of 97.5% in the surgery arm. To exclude a difference of more than 2.5% at 5 years requires 932 patients (allowing for a 10% loss to follow-up).

This trial will generate a wealth of additional data has multiple prospectively planned secondary endpoints, as summarised in [Table 2](#).

11. Patient reported outcome measurers

Patient reported outcomes are of particular interest in this trial and will provide valuable data on the reasons why women choose to take part, or not, and the anxiety related to being actively monitored or, conversely, undergoing surgery. These data will inform other trials of active monitoring that are likely to follow. Whatever the patient reported outcomes, future generations of women diagnosed with low risk DCIS will be in a position to make informed choices, which are not currently possible. The primary quality of life aspect of the trial examines the hypothesis that the psychological well-being of women in the Active Monitoring arm is

Table 2
Primary objective and outcome measures.

<i>Primary objective</i>
<ul style="list-style-type: none"> • To assess whether Active Monitoring is non-inferior to surgery, in terms of ipsilateral invasive breast cancer free survival
<i>Primary outcome measure</i>
<ul style="list-style-type: none"> • Ipsilateral invasive breast cancer free survival time
<i>Secondary outcome measures</i>
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Translational Exploratory assessment of predictive biomarkers

non-inferior to that associated with standard surgical and adjuvant treatments. Patients will be asked to complete questionnaires at different time points that will look at factors that may influence:

- Decision to join, or reject, the trial using the Accept/Decline questionnaire
- Psychological adjustment – anxiety trait and ways of coping. Using the Spielberger State-Trait Anxiety Inventory (STAI) and Brief ways of coping questionnaire

In addition, the impact that surgery and active monitoring may have on anxiety state and general well-being is measured using STAI and SF-36v2 Health Survey.

12. Health economics

If active monitoring is found to be an effective approach in the treatment for centrally 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 and will instead be monitored by annual mammography and be treated as an outpatient, thus avoiding an inpatient stay, and resources may potentially 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 [25].

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 various time points. 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.

13. Recruitment

The SHORE-C team at the University of Sussex held in-depth patient focus groups to explore and demonstrate widespread acceptability of the LORIS trial concept [26]. The lessons learned from the PROTECT trial of observation versus immediate treatment for screen detected prostate cancer have been heeded [27,28]. For example, women are informed about the trial before they receive their diagnosis of DCIS and a DVD is used to provide an even-handed approach to introducing the trial. The language used in the patient information literature and DVD has been carefully worded and, in keeping with contemporary opinion, does not utilise the word ‘carcinoma’ as part of the description of DCIS [29].

14. Trial progress

The trial opened to recruitment in July 2014 and has an in-built feasibility study in which 20 sites will be opened to recruitment in the first instance. Sixty randomised patients are required within 2 years of opening before further sites can join the trial. This tests the ability to open sites in a timely fashion, assesses clinicians’ and women’s agreement to take part, and ensures that adherence to the randomised arm are all sufficient to accrue the full sample size in a timely fashion.

The main challenges so far have been slow site set-up (eleven sites are now open at six months; the mean time for setting up sites in the UK in 2014 is 9.7 months [30]) and the reluctance of NHS Trusts to fund first line VACBs, despite much published evidence that they are the gold-standard for evaluation of microcalcifications and have a better concordance with excision histology than small volume cores [10,11].

The unique central histopathology review process is working well; the one week turnaround for review is

being achieved by the expert pathology reviewers (two of whom are required for each case reviewed, with the third to provide arbitration).

We have encountered a remarkable enthusiasm from our open sites with a clear determination by the multi-disciplinary teams to make this trial a success. As of December 2014, the trial has reached its milestones for site opening, patients registered and patients randomised.

Looking beyond DCIS it is notable that some screen detected invasive cancers, notably tubular carcinomas, are associated with a very indolent course, rarely result in distant metastasis and carry excellent prognosis [31]. These, and similar cancers, represent a further context in which overtreatment is likely. Additional minimisation of overtreatment will require us to address the alternative management of indolent screen detected invasive cancer and is the focus of active discussion within our group.

The LORIS trial is funded by the United Kingdom National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number 11/36/16) and is Sponsored by the University of Birmingham. ISRCTN: 27544579.

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health.

Conflict of interest statement

None declared.

References

- [1] Independent, U.K.P.O.B.C.S., The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380(9855): p. 1778–86.
- [2] Biller-Andorno N. Cancer detection: breast-screening trials are ethical. *Nature* 2014;511(7508):155.
- [3] Gotzsche PC, Jorgensen KJ. The breast screening programme and misinforming the public. *J R Soc Med* 2011;104(9):361–9.
- [4] Kopans DB, Smith RA, Duffy SW. Mammographic screening and “overdiagnosis”. *Radiology* 2011;260(3):616–20.
- [5] CRUK website. <<http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/Incidence-in-situ/>>.
- [6] Rothnie N, An audit of screen detected breast cancers for the year of screening 2011/12 2013, NHS Breast Screening Programme and association of Breast Surgeons.
- [7] CR-UK website, ><http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/incidence/>> [accessed 05.01.2014].
- [8] Evans AJ et al. The detection of ductal carcinoma in situ at mammographic screening enables the diagnosis of small, grade 3 invasive tumours. *Br J Cancer* 1997;75(4):542–4.
- [9] Pinder SE et al. A new pathological system for grading DCIS with improved prediction of local recurrence: results from the UKCCCR/ANZ DCIS trial. *Br J Cancer* 2010;103(1): 94–100.
- [10] Brennan ME et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. *Radiology* 2011;260(1):119–28.

- [11] Yu YH, Liang C, Yuan XZ. Diagnostic value of vacuum-assisted breast biopsy for breast carcinoma: a meta-analysis and systematic review. *Breast Cancer Res Treat* 2010;120(2):469–79.
- [12] Betsill Jr WL et al. Intraductal carcinoma. Long-term follow-up after treatment by biopsy alone. *JAMA* 1978;239(18):1863–7.
- [13] Collins LC et al. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. *Cancer* 2005;103(9):1778–84.
- [14] Sanders ME et al. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. *Cancer* 2005;103(12):2481–4.
- [15] Eusebi V et al. Long-term follow-up of in situ carcinoma of the breast. *Semin Diagn Pathol* 1994;11(3):223–35.
- [16] Dowsett M et al. International Web-based consultation on priorities for translational breast cancer research. *Breast Cancer Res* 2007;9(6):R81.
- [17] Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. *J Pathol* 2011;223(2):307–17.
- [18] Simpson PT et al. Columnar cell lesions of the breast: the missing link in breast cancer progression? A morphological and molecular analysis. *Am J Surg Pathol* 2005;29(6):734–46.
- [19] Wiechmann L, Kuerer HM. The molecular journey from ductal carcinoma in situ to invasive breast cancer. *Cancer* 2008;112(10):2130–42.
- [20] Iakovlev VV et al. Genomic differences between pure ductal carcinoma in situ of the breast and that associated with invasive disease: a calibrated aCGH study. *Clin Cancer Res* 2008;14(14):4446–54.
- [21] Steinman S et al. Expression of cytokeratin markers, ER-alpha, PR, HER-2/neu, and EGFR in pure ductal carcinoma in situ (DCIS) and DCIS with co-existing invasive ductal carcinoma (IDC) of the breast. *Ann Clin Lab Sci* 2007;37(2):127–34.
- [22] Solin LJ et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst* 2013;105(10):701–10.
- [23] Kerlikowske K et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. *J Natl Cancer Inst* 2010;102(9):627–37.
- [24] Rakovitch E, et al., A large prospectively-designed study of the DCIS score: predicting recurrence risk after local excision for ductal carcinoma in situ patients with and without irradiation. *San Antonio Breast Cancer Symposium*, 2014. S5–04.
- [25] Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. *Int J Behav Med* 1997;4(1):92–100.
- [26] Fallowfield L et al. Time for a low-risk DCIS trial: harnessing public and patient involvement. *Lancet Oncol* 2012;13(12):1183–5.
- [27] Donovan JL et al. Development of a complex intervention improved randomization and informed consent in a randomized controlled trial. *J Clin Epidemiol* 2009;62(1):29–36.
- [28] Wade J et al. It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials. *Soc Sci Med* 2009;68(11):2018–28.
- [29] Fallowfield L et al. Low grade Ductal Carcinoma in situ (DCIS): how best to describe it? *Breast* 2014;23(5):693–6.
- [30] Kearney A et al. Opening research sites in multicentre clinical trials within the UK: a detailed analysis of delays. *BMJ Open* 2014;4(9):e005874.
- [31] Rakha EA et al. Tubular carcinoma of the breast: further evidence to support its excellent prognosis. *J Clin Oncol* 2010;28(1):99–104.