King's College Hospital NHS
NHS Foundation Trust

PROTOCOL TITLE:

Prospective Randomised Trial of Digital Breast Tomosynthesis (DBT) Plus Standard 2D Digital Mammography (2DDM) or Synthetic 2D Digital Mammography (S 2D) Compared to Standard 2D Digital Mammography in Breast Cancer Screening

Sponsor
Name of Sponsoring Organisation/s: King's College Hospital NHS Foundation Trust
Name of Sponsor Representative: Rahman Ahmed
Address: Research and Innovation, First Floor 161 Denmark Hill, London, SE5 9RS
Telephone: 0203 299 3841
Email: rahman.ahmed1@nhs.net

Chief Investigator
Name: Dr Michael J Michell, Consultant Radiologist,
Address: Breast Radiology Department and National Breast Screening Training Centre, King's College Hospital
Denmark Hill, London, SE5 9RS
Telephone: 020 3299 3875
Email: michael.michell@nhs.net

Clinical Trial Manager
Name: Natalie Long
Address: Breast Radiology Department
King's College Hospital,
Denmark Hill, London, SE5 9RS
Email: natalielong@nhs.net

Name and address of Investigator(s)
Name: Professor Fiona Gilbert, Head of Department of Radiology, University of Cambridge,
Address: Department of Radiology, University of Cambridge School of Clinical Medicine, Box 218, Cambridge Biomedical Campus, Cambridge, CB2 0QQ
Email: fjg28@medschl.cam.ac.uk

Name and address of Investigator(s)
Name: Professor Kenneth C Young, Head of NCCPM,

Address: Royal Surrey County Hospital
Guildford, GU2 7XX
Email: ken.young@nhs.net

Name and address of Investigator(s)

Name: Professor Stephen W Duffy, Professor of Cancer Screening,
Address: Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square London, EC1M 6BQ
Email: s.w.duffy@qmul.ac.uk

Name and address of Investigator(s)

Name: Dr Mark Pennington
Address: King's Health Economics
P024 David Goldberg Centre
Institute of Psychiatry, Psychology and Neuroscience
King's College London, De Crespigny Park, London SE5 8AF
Email: mark.w.pennington@kcl.ac.uk

Name and address of Investigator(s)

Name: Professor Alastair Gale, Professor of Applied Vision Sciences,
Address: School of Medicine, University of Nottingham, NG7 2UH
Email: a.g.gale@hotmail.com

Name and address of Investigator(s)

Name: Dr Mark Halling-Brown, Head of Scientific Computing,
Royal Surrey County Hospital
Guildford GU2 7XX
Email: mhalling-brown@nhs.net

Name and address of Investigator(s)

Name: John Loveland, Research Physicist,
Royal Surrey County Hospital
Guildford GU2 7XX
Email: john.loveland@nhs.net

Name and address of Investigator(s)

Name: Dr Yan Chen, Director of Applied Vision Research Centre
School of Medicine
University of Nottingham NG7 2UH
Email: Yan.Chen@nottingham.ac.uk

Name and address of Investigator(s)
Name: Dr Asif Iqbal, Research Fellow
Breast Radiology Department and National Breast Training Centre
King's College Hospital,
Denmark Hill, London SE5 9RS
Email: asif.iqbal@nhs.net

Name and address of Investigator(s)
Name: Vivien Milnes, Consultant Radiographer
Breast Radiology Department and National Breast Screening Training Centre,
King's College Hospital
Denmark Hill, London, SE5 9RS
Telephone: 020 3299 3875
Email: vivien.milnes@nhs.net

Statistician
Name: Professor Stephen W Duffy,
Address: Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ
Email: s.w.duffy@qmul.ac.uk

Name and address of Investigator(s)
Name: Helen Edwards, Patient and Public Involvement Group, Independent Cancer Patient Voice
Email: edwardsdevine@hotmail.com

Site Leads

Name and address of Investigator(s)
Name: Dr Keshthra Satchithananda, Co-PI
Address: South East London Breast Screening Programme, King's College Hospital, Denmark Hill, London, SE5 9RS
Telephone: 0203 299 3875
Email: k.satchithananda@nhs.net

Name and address of Investigator(s)
Name: Juliet Morel, Co-PI
Address: South East London Breast Screening Programme, King's College Hospital, Denmark Hill, London, SE5 9RS
Telephone: 0203 299 2052
Email: julietmorel@nhs.net

Name and address of Investigator(s)
Name: Dr Rita McAvinchey,
Address: The Jarvis Breast Centre, Stoughton Road, Guildford, Surrey, GU1 1LJ
Email: rita.mcavinchey@nhs.net

Name and address of Investigator(s)
Name: Dr Nisha Sharma,
Address: Leeds Wakefield Breast Screening Unit, Seacroft Hospital, York Road, Leeds, West Yorkshire, LS14 6UH
Email: Nisha.Sharma2@nhs.uk

Name and address of Investigator(s)
Name: Dr Alexandra Valencia,
Address: Avon Breast Screening Unit, Bristol Breast Care Centre, Beaufort House, Southmead Hospital, Westbury-on-Trym, Bristol, BS10 5NB
Email: alexandra.valencia@nbt.nhs.uk

Name and address of Investigator(s)
Name: Dr Will Teh,
Address: North London Breast Screening Service, Deansbrook House, Edgware Community Hospital, Deansbrook Road, Edgware, Middlesex, HA8 9BA
Email: William.Teh@nhs.net

Name and address of Investigator(s)
Name: Dr Humaira Khan
Address: City, Sandwell and Walsall Breast Screening Service, Breast Unit, Birmingham Treatment Centre, City Hospital, Winson Green, Birmingham, West Midlands, B18 &QH
Email: humairakhan@nhs.net

Name and address of Investigator(s)
Name: Dr Gayle McDonald
Address: Breast Care Centre, Glenfield Hospital, Groby Road, Leicester, LE3 9QP
Email: gayle.mcdonald@uhl-tr.nhs.uk

Study Synopsis

Title	Prospective Randomised Trial of Digital Breast Tomosynthesis (DBT) Plus Standard 2D Digital Mammography (2DDM) or Synthetic 2D Mammography (S 2D) compared to Standard 2D Digital Mammography in Breast Cancer Screening.
Protocol Short Title/Acronym	PROSPECTS
Protocol Version number and Date	Version 4.0 17Aug2020
Is the study a Pilot?	No
Study Duration	Seven years
Methodology	Randomised controlled trial
Sponsor Name	King's College Hospital NHS Foundation Trust
Chief Investigator	Dr Michael J Michell
REC Number	17/LO/0054
IRAS Number	199080
Medical Condition or Disease under Investigation	Breast Cancer
Purpose of Clinical Trial	To measure the cost-effectiveness of DBT and 2DDM compared to standard 2DDM in breast cancer screening
Primary Objective	To compare the cost-effectiveness of breast cancer screening using DBT + 2DDM or S2D with screening using 2DDM by measuring cancer detection rates, interval cancer rates, size and lymph node status of Grade 2 and 3 invasive cancers in intervention (DBT + 2DDM or S2D) and 2DDM (standard care) groups.
Secondary Objective (s)	1.To demonstrate non-inferiority of S2D + DBT compared to 2DDM + DBT in breast cancer screening. 2.To measure the impact of DBT + 2DDM or S2D screening on screening recall rates, benign biopsy rates at diagnostic assessment and at surgery. 3.To measure the effect of DBT + 2DDM or S2D screening compared to 2DDM in patient groups according to breast density, type of screen, age. 4.To develop methods for measuring reader performance with DBT + 2DDM or S2D screening. 5.To carry out retrospective reader studies to measure the effect of other screening strategies – 2DDM vs DBT alone, 2DDM vs 2DDM + limited tomosynthesis views. 6.To compare patient preferences for breast cancer screening with 2DDM + DBT or S2D vs 2DDM.
Number of Subjects/Patients	100,000
Trial Design	Prospective randomised controlled trial
Endpoints	**Primary end-points**

	Invasive cancer detection rates Size and lymph node status of grade 2 and 3 invasive cancers Interval cancer rates Cost of screening with DBT + 2DDM or S2D vs. screening with 2DDM alone Mammography reading time for 2DDM, DBT + 2DDM or S2D **Secondary end-points** 1.Cancer detection rates using DBT + 2DDM compared to DBT + S2D 2.Recall rates Benign biopsy rates at assessment Benign surgical biopsy rates 3.Measurement of cancer detection rates, recall rates in subgroups of women in intervention and control groups defined by breast density, type of screen, age group. 4.Development of a method for measurement of reader performance. 5.Results of retrospective reader studies to compare different screening strategies and costs including DBT alone, 2DDM or S2D + limited tomo views. 6.Measurement of trial participant experience of DBT + 2DDM vs 2DDM or S2D
Main Inclusion Criteria	Women aged 49-71 years attending for routine breast screening.
Statistical Methodology and Analysis	See sections 2.4 and 3.

The trial involves use of a commercially available mammography machine capable of 2DDM and DBT (Hologic Dimensions Mammography machine). The equipment is CE marked and is in use in departments for diagnostic work up mammography for clients recalled following screening. Further information about the equipment can be obtained from the manufacturer's website.

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MHRA	Medicines and Health Regulatory Authority
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
UADE	Unexpected Adverse device Reaction
CAPA	Corrective And Preventive Action

SAR	Serious Adverse Reaction
SADE	Serious Adverse Device Event
GCP	Good Clinical Practice
MHRA	Medicines and Healthcare Products Regulatory Agency

1. Introduction

The accuracy of two view digital x-ray mammography (2DDM), the standard test for breast cancer screening, is limited because of the effect of superimposition of normal breast structures onto a two dimensional image. The mammography signs of breast cancer may be obscured, particularly in women with dense fibro glandular breast tissue (Al Mousa, DS. et al 2014), resulting in delay in diagnosis of cancer. National interval cancer data shows that up to 4000 women per annum (2.88 per 1000 screened) are diagnosed with breast cancer in the interval between screens (Offman, J. & Duffy, S. 2012). Conversely, superimposition of normal tissues may produce features on mammography which are suspicious for cancer and lead to unnecessary recall for further diagnostic tests. National screening data for 2012/2013 show that of 2.3 million women screened, 79000 (3.4%) without breast cancer were recalled to specialist diagnostic assessment clinics (Centre for Cancer Prevention, 2014).
DBT is an x-ray mammography technique which involves acquiring multiple low dose projections over a limited angular range (less than 50 degrees). These projection images are reconstructed into a set of images consisting of parallel planes, typically 1mm apart throughout the breast. Three dimensional information is provided for the reader, overcoming many of the interpretation problems associated with 2DDM. Several studies have demonstrated improvement in the accuracy of DBT in the diagnostic setting (Brandt, K. et al 2013 & Morel, J. et al 2014) Published data from studies of DBT combined with 2DDM in screening have demonstrated increased rates of invasive cancer detection, cancers detected at a smaller size and decreased false positive recall rates (Skaane, P. et al 2013, Ciatto, S. et al 2013 & Friedwald, S. et al 2014). However, there may be increased costs associated with the technology, image data storage and longer reading time (Bernardi, D. et al 2012).

As a result of recent technical developments, a two dimensional mammography image can be produced by processing the tomosynthesis image data. Synthetic 2D (S2D) trial data show that the accuracy of DBT + S2D may be the same as that achieved with DBT + 2DDM.

The primary aim of this trial is to assess the impact of the addition of DBT to 2DDM in routine breast cancer screening compared to 2D mammography. 100 000 women will be recruited using NHS screening sites with DBT ready mammography equipment. At each site, through a clinic randomisation process, half the trial participants will undergo standard 2DDM (the control group) and half will undergo 2DDM and DBT (the study group). Synthetic 2D images will be produced for all women in the intervention group. A secondary objective of the trial is to compare the accuracy of DBT + 2DDM with DBT + S2D. For each woman in the intervention group, one reader will view DBT + 2DDM, and the other reader will view DBT + S2D. This will enable a non-inferiority test to be applied to DBT + S2D vs DBT + 2DDM.

We plan to use DBT in addition to 2DDM in the intervention group because:

- Most previous trials demonstrated increased sensitivity and specificity by using DBT in combination with 2D imaging rather than as a replacement.
- By using both 2D and DBT in the study group, we will be able to review the display of the same cancer in the two techniques.

One concern about using DBT in conjunction with 2D imaging is the increase in radiation dose. We conservatively estimate the mean glandular radiation dose of 4mGy in the control group and 9mGy in the study group. In other words, DBT imaging requires slightly more than double the dose of 2D imaging. A recent study of (Yaffe & Mainprize 2011) has shown that benefits of screening with mammography greatly exceed the detriment due to the radiation. Using similar calculations we estimate that the ratio

of lives saved and lost due to radiation in the 2DDM screening arm will be in the range 150-300 to 1. The higher dose in the study group is expected to lead to greater benefit and greater detriment. In order for the extra benefit to exceed the extra detriment of using DBT in the study group there will need to be a very small (0.45% to 0.9%) increase in lives saved. In practice we expect a larger benefit that this.

- Health need: the effectiveness of 2DDM in detection of invasive breast cancer has improved over the last twenty years as demonstrated by a decrease in interval cancer rates (cancers occurring between routine three yearly screens) (Offman, J. & Duffy, S. 2012). This improvement is a result of the introduction of two view mammography, digital mammography and improvements in film reading performance. However, the most recent published interval cancer rates of 2.85 per 1000 women screened demonstrates the limited sensitivity of 2DDM in cancer detection. Published data from studies of DBT and 2DDM in screening in Europe and North America demonstrate an increased invasive cancer detection rate of 40-48% compared to 2DDM alone (Skaane, P. et al 2013 & 2014, Ciatto, S. et al 2013, Friedwald, SM. Et al 2014 & Zackrisson, S. et al 2014). Data from this study will demonstrate whether such an improvement in sensitivity is achievable in the NHSBSP, whether cancers can be detected at a smaller size, and prognostic features of screen detected and interval cancers will be used to model whether there would be a greater reduction in breast cancer mortality from screening with 2DDM plus DBT compared to 2D alone. Data will also demonstrate the effect on false positive recalls in the NHSBSP. Published results show that this may be decreased by 15-20% with the use of DBT.
- Economic analysis: The study will demonstrate whether replacing standard 2DDM with DBT (and S2D) represents an efficient use of NHS resources, either because DBT reduces overall cost or because the additional health benefits of greater sensitivity and specificity justify the additional cost.
- Sustained interest: DBT may have a major impact on the effectiveness and the cost of screening. Data from this study will help decide the optimum strategy for using DBT in routine screening in the NHS.
- Development of research area: results from this study will help identify which groups of women will benefit from screening with DBT.
- Scientific knowledge: this study will advance our understanding of the effect of DBT on the characteristics of screen detected cancers, whether more biologically significant cancers are found when smaller and at an earlier stage, and whether more low grade cancers are diagnosed, increasing the problem of over diagnosis.

Literature Review.

1. The technical aspects of digital breast tomosynthesis have been reviewed (Sechopoulos, I. 2013, Gilbert, FJ. 2010).

2. Clinical studies measuring the accuracy of DBT compared to 2DDM in breast cancer detection have been reviewed (Houssami, N. & Skaane, P. 2013 & Alakhras, M. et al 2013). These studies measured the performance of readers in the interpretation of test sets or clinical series of cases, either symptomatic or screening recalls, usually with a high proportion of cancers. The data demonstrates that two view DBT has at least equal or better accuracy than standard 2DDM, and that the addition of DBT to 2DDM improves reader accuracy (Michell, MJ. et al 2012, Rafferty, EA. et al 2013, Gilbert, FJ et al 2014).

3. Screening Studies using DBT.

A systematic search of the literature has been performed (medline and embase databases, 2010 – 2015, search terms ‘tomosynthesis’ ‘screening’).

A review of the literature identifies 8 retrospective studies (Lourenco, AP. Et al 2015, Durand, MA. Et al 2015, McCarthy, AM. et al 2014, Greenberg, JS. et al 2014, Friedwald, SM. et al 2014, Destounis, S. et al

2014, Haas, BM. et al 2013 & Rose, SL. et al 2013) and 3 prospective studies (Ciatto, S. et al 2013, Skaane, P. et al 2013, 2014, Zackrisson, S, et al 2014) of DBT in addition to 2DDM in screening. All the studies report an increase in cancer detection when using DBT. In the three prospective studies and the largest retrospective study the increase in cancer detection rate ranges from 27% - 51%. This is due to an increase in invasive cancer detection with no significant change in DCIS rate. Most of the studies show a decrease in the false positive recall rate of 15-20%. In one study the recall rate increased from 2.6 to 3.8% but the PPV remained unchanged indicating that the increase in recall rate from a very low base was matched by an increase in cancer detection (Zackrisson, S. et al 2014). There is limited data on the pathological characteristics of the additional cancers detected by DBT. In the Oslo study, 60% of the additional cancers were Grade 1 and 40% were Grade 2 or 3 (Skaane, P. et al 2013).

There remains debate over the use of DBT in large scale population breast screening programmes because of uncertainty about costs of implementation including reading time, data storage and transfer and the effect of DBT on the efficacy of screening and over diagnosis (Gilbert, F. et al 2016). The biological significance of DBT screening detected cancers can be demonstrated by examining their prognostic features and interval cancer rates (Evans, A. 2015).

- We propose a prospective randomised trial to measure the effect on cancer detection and recall rate of screening with DBT + 2DDM or S2D compared to 2DDM alone. Data on the numbers and pathological characteristics of the cancers diagnosed by screening and those found as interval cancers will be used to calculate the effect of DBT on the numbers of breast cancer deaths prevented and the number of Quality Adjusted Life Years (QALYs) gained.
- The cost implications of using DBT in routine screening relating to technology, IT and data storage, image reading time and assessment practice will be calculated. In combination with the estimated gain in QALYs, the cost-effectiveness in terms of the additional cost per QALY will be calculated.
- The data will be analysed to measure any differences in the effect of screening with DBT + 2DDM or S2D in different patient subgroups identified by breast density, type of screen and age.
- Retrospective reader studies will be carried out to assess other mammography screening strategies including use of synthetic 2D mammography.
- The target population for this trial is women aged 49-71 years attending for routine mammography screening.
- The new technology being evaluated is digital breast tomosynthesis (DBT).
- Patient experience of DBT + 2DDM or S2D vs 2DDM will be assessed.

The comparator technology is two dimensional digital mammography (2DDM) which is the current standard test for routine breast cancer screening.

2 Trial Objectives, Design and Statistics

2.1. Trial Objectives

Primary objectives.

To compare the cost – effectiveness of breast cancer screening using DBT + 2DDM or S2D with screening using 2DDM by measuring cancer detection rates, interval cancer rates, size and lymph node status of Grade 2 and 3 invasive cancers in intervention (DBT + 2DDM or S2D) and 2DDM (standard care) groups.

Secondary objectives.

1. To demonstrate non-inferiority of DBT + S2D compared to DBT + 2DDM.
2. To measure the impact of DBT + 2DDM screening on screening recall rates, benign biopsy rates at diagnostic assessment and at surgery.
3. To measure the effect of DBT + 2DDM screening compared to 2DDM in patient groups according to breast density, type of screen, age.
4. To develop methods for measuring reader performance with DBT + 2DDM screening.
5. To carry out retrospective reader studies to measure the effect of other screening strategies – 2DDM vs DBT alone, 2DDM vs DBT + synthetic 2D, 2DDM vs 2DDM + limited tomosynthesis views.
6. To compare patient preferences for breast cancer screening with 2DDM + DBT vs 2DDM.

Primary end-point.

Invasive cancer detection rates
Interval cancer rates
Size and lymph node status of grade 2 and 3 invasive cancers
Cost-effectiveness of screening with DBT + 2DDM or S2D vs screening with 2DDM.

Secondary end-point.

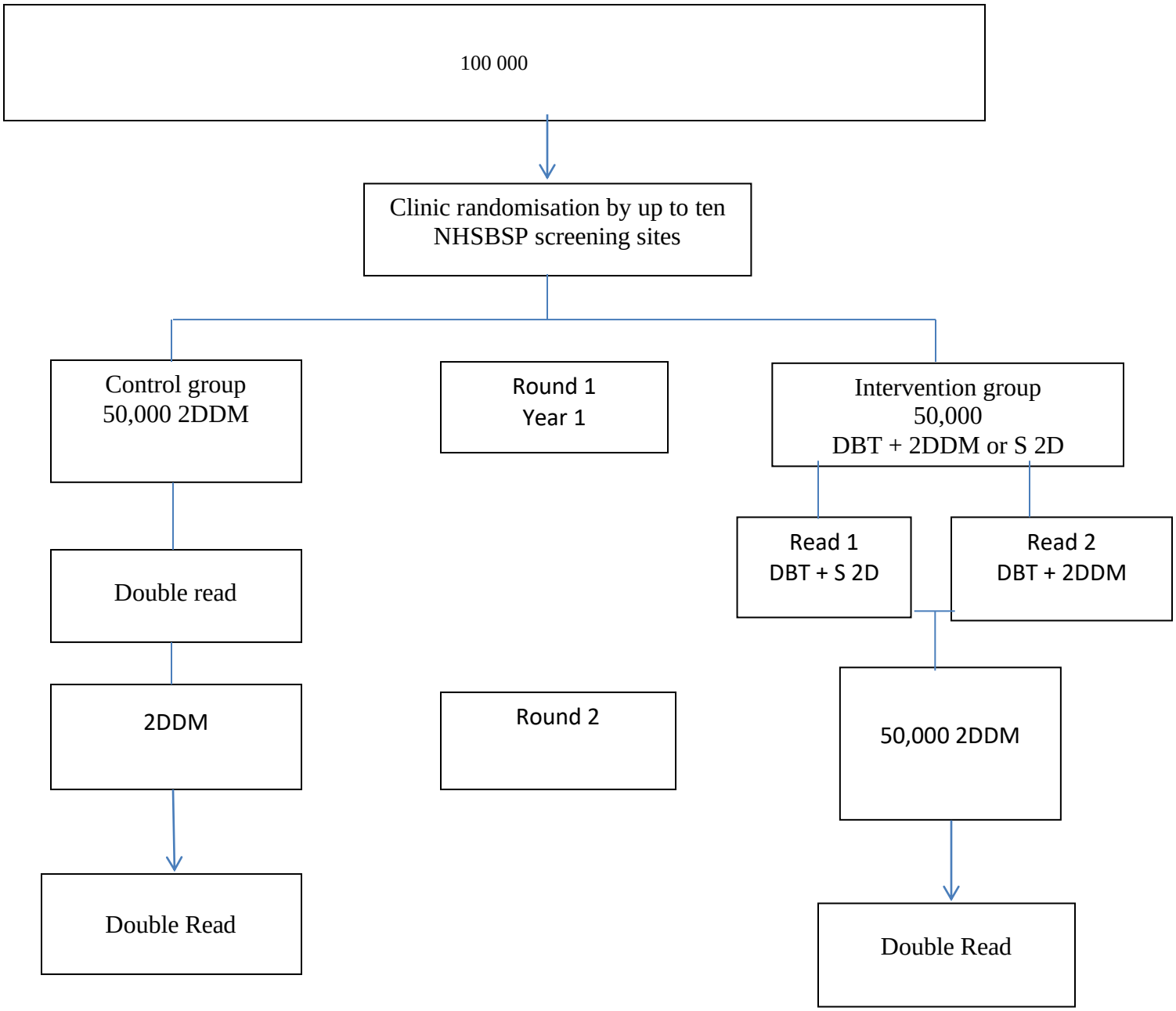
1. Measurement of invasive cancer detection rates using DBT + S2D vs 2DDM
2. Recall rates
   Benign biopsy rates at assessment
   Benign surgical biopsy rates
3. Measurement of cancer detection rates, recall rates in subgroups of women in intervention and control groups defined by breast density, type of screen, age group.
4. Development of a method for measurement of reader performance.
5. Results of retrospective reader studies to compare different screening strategies including 2DDM + synthetic 2D, DBT alone, 2DDM + limited tomo views.
6. Measurement of trial participant experience of DBT + 2DDM vs 2DDM.

2.2 Trial Design

Randomised controlled trial.

Women aged 49-71 years attending for routine mammography screening will be randomised by batch/clinic to either standard care group (2DDM) or intervention group (DBT + 2DDM or S2D). The images will be double read by NHS BSP film readers fulfilling NHS BSP QA criteria for film reading and who have undergone training in DBT image interpretation. The results of film reading will be recorded on the National Breast Screening Computer System (NBSS) and then complete data (with surgical and pathology data where appropriate) will be downloaded for statistical analysis. The initial trial recruitment period will be the length of time required to reach the recruitment target of100,000 women by up to ten NHSBSP screening centres. Some women who participate will be invited to participate again when invited for their next routine screen three years later. Interval cancer data will be collected as per routine by the screening centres in collaboration with Cancer Registries and QA Reference Centres.

2.3 Trial Flowchart


100 000
Clinic randomisation by up to ten NHSBSP screening sites
Control group 50,000 2DDM
Round 1 Year 1
Intervention group 50,000 DBT + 2DDM or S 2D
Read 1 DBT + S 2D
Read 2 DBT + 2DDM
Double read
2DDM
Round 2
50,000 2DDM
Double Read
Double Read

	Control 50 000	Intervention 50 000
Inv ca	311	435
IC Gd 2 3	232	325
Mean size (mm)	18	14 (95% power)
Interval ca	143	93
Interval ca /1000	2.85	1.85 (90% power)

2.4 Trial Statistics

1. Impact of DBT on breast cancer deaths

The trial was originally conceived to show a difference between study and control groups in interval cancer rates. However, there is a clear need for a result indicating the additional benefit of DBT screening before the interval cancers are observed. We propose to base formal significance testing at this earlier stage on the harvest of invasive cancers detected at screening and on the pathological size of these cancers. In order to avoid overestimation of the likely benefit from over diagnosis or length bias, we will test for a difference in size between the Grade 2 and 3 cancers detected by DBT and 2DDM compared to 2DDM. A preliminary estimate of the effect of DBT on reducing breast cancer deaths compared to standard 2DDM will be calculated using the difference in cancer detection rates and the prognostic features of the screening detected cancers in the study group (DBT & 2DDM) compared to the control group (2DDM). This will be calculated using only the invasive grade 2 and 3 cancers to give a conservative estimate, and then using all cancers, potentially giving an anticonservative estimate. The true effect is likely to lie between the two. At three to five years following recruitment, the interval cancer rates will be compared between the two groups. Thereafter, a more definitive estimate of the expected breast cancer deaths avoided will be calculated using both screen-detected and interval cancers. Projected mortality will be estimated using the approaches developed by Day and Duffy (1996), Duffy et al (1997) and Chen et al (1997).

2. Non-inferiority of DBT + S2D vs DBT + 2DDM.

To establish safety of the use of DBT+synthetic 2D, we propose a matched non-inferiority analysis within the DBT arm of the trial. If the results for DBT+FFDM are cross-tabulated with those for DBT+synthetic 2D for the cancers only, the following table would be observed.

Recalled by DBT+synthetic 2D	Recalled by DBT+FFDM		
	No	Yes	Total
No	A	B	a+b
Yes	C	D	c+d
Total	a+c	b+d	N

In practice, a will be equal to zero, since we are only considering the screen-detected cancers here. We need a sufficient number of cancers to give 90% power, in the presence of true equivalence, to have a 95% confidence interval on the difference between the two sensitivities which does not extend beyond 10%, i.e. to rule out the possibility that DBT+synthetic 2D is more than 10% less sensitive than DBT+FFDM. In algebraic terms,

$$P\left\{\frac{b+d}{N}-\frac{c+d}{N}+1.96\times SE\left(\frac{b+d}{N}-\frac{c+d}{N}\right)<0.1\right\}=0.9$$

That is,

$$P\left\{\frac{b-c}{N}+1.96\times SE\left(\frac{b-c}{N}\right)<0.1\right\}=0.9$$

Assuming multinomial variances and covariances for b, c and d with total N, the variance of (b-c)/N is

$$V\left(\frac{b-c}{N}\right)=\frac{1}{N^2}\left\{\frac{c(N-c)}{N}+\frac{b(N-b)}{N}+2\frac{bc}{N}\right\}$$

This simplifies to

$$V\left(\frac{b-c}{N}\right)=\frac{1}{N^3}\{N(b+c)+(b-c)^2\}$$

Under the equivalence assumption, the expectation of the second term is zero, so that

$$V\left(\frac{b-c}{N}\right)=\frac{(b+c)}{N^2}$$

and its standard error is the square root of this. Substituting in the power equation above and dividing throughout by the standard error, we have approximately

$$P\left\{z+1.96<\frac{0.1N}{\sqrt{b+c}}\right\}=0.9$$

Where z is a standard normal random variable. From the properties of the standard normal distribution, this solves to give

$$\frac{0.1\sqrt{N}}{\sqrt{p}}-1.96=1.28$$

where p is the proportion of disagreements between the two modalities. If we assume conservatively that p=0.2, this gives N = 210, that is we would require 210 cancers in all to establish non-inferiority. In fact we will have more than double this number so there is more than adequate power to establish non-inferiority of DBT+synthetic 2D compared to DBT+FFDM.

3.Universal FFDM only at second round

Again, due to pressures on resources and capacity, specifically screening time, it is unlikely to be feasible that a second round of DBT can take place in 50,000 subjects. We therefore propose that the second round in both arms be with the standard of care in the NHSBSP, FFDM alone. This may in fact have an unexpected benefit. If the harvest of cancers at the second round is lower in the intervention arm, this will establish that DBT results in detection of cancers that would have been diagnosed with the standard of care in any case but would have been detected three years later, likely at a substantially later stage.
We assume that the yield of cancers in the control group will be 8 per thousand as consistently observed in the NHSBSP. We might reasonably expect this to be 6 per thousand in the intervention arm. With 50,000 per arm, we will have 90% power to detect such a difference as significant (5% significance, 2-sided testing). This study size will also have 80% power to detect a more modest difference, assuming 6.5 per thousand in the intervention arm.

2.5 Economic analysis

Economic evaluation of DBT

We will undertake a detailed study of the cost of screening with 2DDM and with DBT and either S2D or 2DDM. Capital and maintenance costs related to screening technologies will be obtained from the manufacturers or finance departments at the screening centres and amortized appropriately according to predicted lifetime. Staff costs and overheads for screening centres and image reading centres will be derived from centre finance departments. The time taken to record images with each screening modality, and the time to read images will be determined and combined with centre costs to estimate a total cost per mammographic screen for each of the screening centres in the trial. Costs associated with follow-up of a positive screen will be determined in consultation with screening centres. Patient costs will be estimated on the basis of typical attendance times valued at average gross wage rate along with estimates of average travel costs.

We will undertake a cost-utility analysis of DBT + S2D (or 2DDM) compared to current practice (2DDM). The primary analysis will consider an NHS perspective and include future related costs of screening (diagnosis and treatment of Breast cancer). A societal perspective which includes patient costs of attending screening and follow-up will be examined in a sensitivity analysis. The primary analysis will consider the costs and consequences of Breast screening with either modality over the trial follow-up period. We will estimate the impact on health and treatment costs of cancers detected by predicting treatment costs and mortality according to age and prognostic factors at diagnosis. Mortality will be weighted for quality of life to estimate the Quality Adjusted Life-Years (QALYs) lost to Breast cancer in each arm. A QALY is measure of health outcomes which combines longevity and quality of life. If overall costs are higher in the DBT arm the data will be combined to estimate an Incremental Cost-Effectiveness Ratio (ICER) for DBT and allow comparison against accepted thresholds of £20,000 to £30,000 per QALY. The trial data will be bootstrapped (a resampling technique to quantify the impact of uncertainty in the data) and the results presented as a

Cost-Effectiveness Acceptability Curve (CEAC). The CEAC plots the probability an intervention is cost-effective according to the value placed on the health outcome and after allowing for sampling uncertainty.

In addition to this analysis we will build a simulation model of Breast cancer. The model will utilize data on costs, sensitivity and specificity of each screening modality taken from the trial data along with data from the literature on the natural progression of Breast cancer to estimates costs associated with screening and treatment of Breast cancer and quality adjusted life-expectancy over women's lifetimes. The model will fully incorporate uncertainty around parameter estimates and the main outputs will be the mean ICER across simulations and the CEAC.

3. Sample Size, Selection and Withdrawal of Subjects

Sample Size:
We propose a sample size of 100,000 women aged 50-70 years attending screening: 50,000 undergo DBT and 2DDM or S2D screening (the intervention group), 50,000 undergo 2DDM (the standard care group). The sample size is based on the numbers required in the study and control groups to demonstrate with 90% power a difference in interval cancer rates of 1.85/1000 (DBT & 2DDM) compared to 2.85/1000 (2DDM), at 5% significance level with 2-sided testing. With approximately 50,000 per arm, we expect 93 interval cancers in the study arm and 143 in the control arm, which will confer the required power of 90%.
As noted above, we will also base formal significance testing at the earlier stage when the screen-detected cancers are available but interval cancers are not, on the harvest of invasive cancers detected at screening and on the pathological size of these cancers. In order to avoid overestimation of the likely benefit from over diagnosis or length bias, we will test for a difference in size between the Grade 2 and 3 cancers detected by DBT and 2DDM compared to 2DDM. On the basis of national screening programme results, we would expect 311 invasive cancers in the 2DDM group of which 232 would be Grade 2 or 3, with an average size of 18 mm (SD 13 mm). If we assume that an additional 40% of grade 2-3 tumours would be detected in the DBT arm and that these would be substantially smaller, reducing the overall average to 14 mm, we would have 95% power to detect this difference as significant.

3.1 Inclusion Criteria

- Women aged 49-71 years attending for routine breast screening using x-ray mammography.
- Able to provide informed consent.

3.2 Exclusion Criteria

- Women aged less than 49 years or more than 71 years (these women may already be taking part in the National Age Extension Screening Trial)
- Women unable to provide informed consent.

3.3 Criteria for Premature Withdrawal

Women who consent participate in this trial will undergo either 2DDM or 2DDM + DBT. Following mammography, there are no further trial specific investigations and we do not therefore foresee instances of premature withdrawal from the trial.

4. Study procedures

4.1 Informed Consent Procedures

- All eligible women who are to be invited to participate in the trial will be sent written information about the trial. . This information will either be sent by post or emailed.
- The majority of potentially eligible women will be contacted by telephone prior to screening appointment, she will be asked whether she has received the written trial information and whether she is willing to participate in the trial.
- Women will be advised to read all the information including the consent form and make a decision of whether to participate prior to attendance for screening.

There are a number of options available for consenting as outlined below:

Option 1: e-consenting - Women receive the trial information and/or are contacted by a member of the PROSPECTS team. If a women decides that she would like to consent, she may visit the PROSPECTS website or go directly to the e-consenting portal URL (details of this are provided on the PIS). At the end of the consent form, there will be an option to enter an email address where a confirmation email and her consent form will be sent, alternatively she can contact the trial site to request a copy of the form to be posted. If personal electronic devices and the internet are not accessible, the e-consenting process may be possible by using a PROSPECTS iPad/Tablet at sites that have adequate time and space available to facilitate this. Women may contact the site if she requires assistance with this. If a women has e-consented less than 48 hours prior to her appointment, she must bring confirmation with her, as the list of those consented is exported in advance.

Option 2: Over the phone paper consent - If women are contacted by the research team over the phone, she may be given the opportunity to consent over the phone either at the initial time of contact or at a later date arranged. She must have a paper consent form which she may have received through the post or electronically. She may complete the form whilst on the phone to the research team and must bring this form with her or scan the completed form to the research team in advance. The research team will keep a record of those who have consented over the phone which will be shared with relevant sites. The names on any paper forms which are brought in will be checked against the list provided by the research team, collected and scanned. The scanned pdf's will be sent to the research team. They will then populate with an electronic signature and these forms will be saved. If women would like a copy of their signed form, they will request this by contacting the research team using the details provided on the PIS.

Due to the COVID-19 pandemic, at some trial sites, infection control regulations may not allow paper forms to be used at all. In these cases, e-consenting must be used as an alternative.

Option 3: Women has pre-signed a consent form, but has had no contact with the research team - In cases where the research team have been unable to contact a women and she arrives with a completed consent form, the mammography staff will simply verify the signature is their own and countersign. If option 3 occurs in sites where paper forms are not allowed, the option to e-consent may be available if time allows, otherwise she will not be allowed to join the trial.

Option 4: Women has not had contact with the research team and has not consented – Some sites will have adequate space and time available to facilitate a face to face consenting option. When a women arrives and time allows, she may be provided with trial information and a trial conversation may take place. Resources may be available at these sites such as iPad/tablets, PIS, PIL and paper consent forms (subject to site specific infection control policy). If a women decides to consent, the site staff can facilitate this process and countersign the paper consent form or provide an electronic device for e-consenting.

- If a woman declines to participate, she will be offered standard 2D digital mammography screening.
- If a woman accepts the invitation to participate, she will undergo either standard 2DDM or 2DDM/S2D and DBT according to the clinic randomisation procedure. After the first 25,000 women have undergone 2DDM and DBT, women entered into the interventional arm will undergo DBT and S2D.
- Women will no longer be provided a copy of the consent form at their appointment, if a women wishes to receive either an electronic or paper version of the consent form, she must contact the site using contact details on the PIS.

Prospects Trial Pilot Project

1. *Background*

   The PHE RAC outcome letter (12-7-2017) and the PHE ODR letter of 01-08-2017 identified concerns regarding the trial participant consenting process as described in the original trial protocol v1.0 14-12-2016. The PHE RAC have said that many women attending for routine breast screening have not read the information leaflet provided and are therefore unlikely to have read the written information about the trial in the PIS. Potential trial participants should be given the opportunity to ask questions about the trial at the time of attendance for screening. The trial pilot project has been developed

   - to address these concerns and to identify the optimal method for obtaining informed consent from potential trial participants.
   - to ensure that the consent process does not interfere with the efficient running of the screening clinics.
   - to develop a consent process which can be used at trial sites across the UK and which will enable sufficient numbers of participants to be recruited into the trial.

2. *Method*

   A three month pilot project is proposed. This will be run at the static screening site 104 Denmark Hill, part of the South East London BSP. Potential trial participants will be

invited to attend the trial clinics on three days per week (two days to be non-trial clinics).

The NBSS system with the PROSPECTS amendment will be used to identify and invite women aged 50-67 years to the trial clinics. These women will receive written information about the trial (PIS) and the consent form together with the routine screening information sent with screening appointment. On attendance at the trial screening clinic, the reception and consent process will be as follows:

i) Receptionist checks the client's identity (as per normal practice)
ii) Receptionist checks whether client has received trial information
iii) Receptionist asks the client if they wish to participate in the trial
iv) If YES, the client's screening sheet is marked accordingly, the client is taken to the mammography screening room by the radiographer and signs the consent form. The client undergoes either standard 2DDM screening or 2DDM + DBT according to the clinic randomization
v) If NO, the client's screening sheet is marked accordingly , the client is taken to the mammography screening room to undergo standard 2DDM screening
vi) If the client has questions about the trial which she would like to discuss further in order to make an informed decision about trial participation, she will be offered a discussion with a member of the CRN (Clinical Research Network) team or radiographer who will be in attendance at the trial clinics. At the end of this consultation the client is invited to decide whether to participate in the trial and the client screening sheet is marked accordingly as in 4. and 5. above. The client then proceeds to either standard screening with 2DDM or trial screening with 2DDM or 2DDM+DBT according to clinic randomization.
Note: the CRN team member will be fully briefed on the trial and anticipated questions. However, if she is unable to answer a question, she will have direct phone contact with a member of the research team

3. *Pilot project participant estimates and outcome measures.*

1.Number of women attending trial clinics = 70/day

= 210/week
= 800/month
Total = 2400

2. Outcome measures

- no. of women who confirm that they have received PIS and Consent form

- no. of women who consent to trial participation (step 4)

- no. of women who decline trial participation (step 5)

- no. of women who take up the offer of consultation to discuss trial with CRN staff member

- no. of women who consent following consultation

- no. of women who decline to participate following consultation

- measure of client satisfaction with provision of Trial Information

The results of the Pilot project will be used to decide on the optimal trial consent process and inform other trial sites prior to recruitment.

4.2 Randomisation Procedures

All the participating screening centres will identify clinics which could be used for the trial. The clinics will be randomised in advance to either standard 2DDM or intervention 2DDM and DBT.

4.3 End of Study Definition

The end of the study will be at the end of data collection for trial participants. This will be 5 years following the end of the second round of screening recruitment (i.e. the time taken to collect interval cancer data).

5. NHS Breast Screening Services – Trial Procedures

5.1 Mammography Examinations

Mammography examinations on trial participants will be carried out at NHS Breast Screening Services which have mammography equipment capable of both 2DDM and DBT. Physics testing and Quality Assurance will ensure that the image characteristic of mammograms at the different sites are equivalent.

5.2 Image Storage

Mammography images will be stored on the local service PACS (processed data) and the raw image data will be stored on a separate local storage device. Raw image data will then be downloaded and transferred to a central trial image data store. This will be used for subsequent analysis and reader studies (see secondary trial objectives). Images transferred to the central trial image data store will be deindentified and assigned a unique trial number.
(see document – Management Protocol for the PROSPECTS Trial Data and Image Database. V1.8 21.01.2019)

5.3 Mammography Film Reading

All mammograms of trial participants will be independently double read according to NHS BSP standard practice. The film readers will be NHS BSP approved readers, either radiologists, breast clinicians or specialist practitioner radiographers. All trial film readers will have undergone NHS BSP approved specialist training in interpretation of DBT images.

5.4 Results of Mammography Film Reading

The results of film reading for each case will be stored on the NHS BSP computer system (NBSS) as per routine practice. A field on the NBSS screening client software will be used to identify the screening client as a trial participant and which arm of the trial she has entered (standard 2DDM or intervention 2DDM and DBT). When the data collection on NBSS is complete, including where appropriate results of further tests for those recalled to assessment, and details of surgery, surgical histology and further treatment, data for trial participants will be anonymised, downloaded and stored on a central trial database for analysis.

5.5 Data Recording/Reporting

The results of screen reading and, where appropriate, diagnostic assessment, treatment and histology will be recorded as per routine practice on the local NHSBSP computer system. When the data is complete it will be downloaded in an anonymised format and each trial case will be given a Unique Trial Number. The trial data, with no personal identifiable information, will then be uploaded onto the central trial database for analysis.

5.6 Image transfer to other sites

The mammogram images of the intervention and standard care groups will be anonymised and transferred to the central trial image data store. Each trial participant's images will be linked to their Unique Trial Number.
(see document – Management protocol for the PROSPECTS Trial Data and Image Database V 1.8 21.01.2019)

5.7 Trial site service quality
Potential impact of trial participation on service quality.

Screening attendance - there is no evidence that participation in the trial by a service will affect screening attendance uptake.

Film reading – reading time will be increased for women in the intervention arm who undergo 2DDM + DBT by approx. 2X. Additional funding will be provided to the trial sites to provide the additional film reading capacity required. The site PI and data manager are responsible for ensuring that the additional film reading time is provided in order to avoid breeches of the screen to normal and screen to assessment waiting time targets.

Assessment – most published studies show that fewer women who undergo 2DDM+DBT are recalled for assessment compared to women who undergo standard screening. It is not anticipated therefore that additional assessment capacity will be required.
Most women recalled following DBT for a soft tissue lesion will not require further mammography.

Diagnostic BX – most soft tissue lesions detected by 2DDM/DBT will be readily visible on US and amenable to US guided BX. A small proportion (approx. 5%) may not be US visible and these lesions will require tomosynthesis guided BX in order to obtain a diagnosis.

Service quality monitoring -

- The site PI and data manager are responsible for service quality monitoring.
- Service quality monitoring data will be collated by the Trial Coordinator

Service quality measures -

- Screen to normal result
- Screen to assessment clinic appointment
- Screening round length adherence to targets

Data to be provided quarterly including the three months prior to beginning recruitment. These data should be regularly submitted to PHE to ensure that service delivery of the target population is not compromised.

Screening centres involved in the trial

To ensure that centres participating have adequate capacity to commence the trial, PHE would expect that the following programme targets have been met for the previous 2 quarters and that there are no known concerns about service delivery or programme management. Units should achieve the following targets:

- Screen to normal results
- Screen to attendance at assessment
- Technical repeat/recall rates
- Screening round length

<u>Failure to achieve programme targets</u>

If participation in the trial is having a sustained impact on maintaining service delivery (with failure to achieve 2 or more of the standards above for more than 2 consecutive quarters), PHE will consider whether it is appropriate for the centre to continue in the trial if the failure is directly attributable to trial participation. This will be discussed with the Trial PI and may result in a centre ceasing trial participation until it is achieving standards satisfactorily.

6. Assessment of Safety

6.1 Risk from Ionising Radiation

Radiation dose to participants

Round 1

The first 50,000 woman will undergo either 2-view digital mammography (DM) (control group) or 2-view digital mammography plus 2-view tomosynthesis (DBT) (intervention group) during screening. The estimated mean glandular dose for typical breasts (50 to 60mm thick) for 2-view DM using this technology is 4 mGy. The estimated mean glandular dose for typical breasts (50 to 60mm thick) for 2-view DBT is up to 5 mGy. The data from the first 50,000 women will be reviewed and if it shows that synthetic 2D imaging + DBT is equivalent to standard 2D + DBT imaging in terms of cancers detected, synthetic 2D imaging will be used instead of the standard 2D imaging with DBT in the intervention group thereafter.

The National DRL is 3.5 mGy for oblique view DM and this can be approximately doubled for comparison with 2-view DM. There is currently no DRL for DBT as the technique is new, but should not exceed existing NDRL's for standard DM. The entire dose for the DBT imaging is additional to normal screening procedures in the UK but has become routine in some parts of the USA.

Round 2

In the second round () the women in the control group and the interventional group will be invited to undergo 2DDM as for the control group in round 1 with the same radiation doses. Therefore at worst, the same dose constraint of 14mGy should be applied, but doses are expected to be considerably lower.
Table 1; Summary of doses on control and intervention groups

	Mean glandular dose to typical breasts (50-60mm thick)	
	Control group	Intervention group
Round 1	4 mGy	9 mGy or 5 mGy*
Round 2	4 mGy	4 mGy

*.

The radiation doses involved in mammography examinations by the NHS Breast Screening Programme are routinely monitored and have recently been reviewed to take account of the introduction of digital imaging which has lowered doses by about 25% on average.(Young and Oduko, 2016)

Risk assessment

The additional lifetime risk of inducing a breast cancer due to a single two view DM examination in this study is estimated to be approximately 1 in 35,000 for exposures between the ages of 50 and 70 assuming an induction rate of 2 to 12 per million per mGy depending on age at exposure calculated by Warren et al (2016). Warren et al derived their risk factors from a report by the Health Protection Agency (HPA) (Wall et al, 2011).

For this research protocol if the dose constraint were to be met, the total mean glandular dose would be 14mGy per round, giving rise to an estimated 1 in 10,000 total risk of cancer induction (assuming an induction rate of 7 per million per mGy) in round 1.
The additional risk of cancer induction to the control group would be zero, with an additional risk of 1 in 29,000 from the 2 view digital tomosynthesis to the intervention group.
Based on actual dose data, maximum risk is estimated to be 1 in 16,000 total risk of cancer induction based on 2 view digital mammography and tomosynthesis (9mGy total MGD).

Women in round 2 of the study will have no additional risk compared to standard care.

The level of radiation risk in either arm of the study is classified as very low by the HPA (HPA leaflet "X-rays: how safe are they?).

Overall the additional doses involved in this protocol are very low in the intervention group and the total dose in round 1 is just above the upper end of the range currently accepted for routine two view breast screening examinations (i.e. 7 mGy) and comparable to a few months to a year of background radiation.

Benefit of additional dose

Warren et al (2016) showed that the mortality benefit from screening in the UK with 2-view DM greatly exceeds the detriment from the radiation risk (by a factor of about 150-300). The women participating in the intervention group are expected to have a benefit from the additional exposure involved in obtaining the DBT images. Gilbert et al (2016) recently reviewed the evidence for using DBT imaging in screening. Four major studies showed increased detection of invasive cancers when DBT was used along with a reduction in the number of unnecessary recalls in three of the studies. This improvement in the sensitivity of screening is expected to lead to fewer interval cancers and improved survival from breast cancer in the screened population although there is as yet no direct evidence for this. In order for the extra benefit to exceed the extra detriment of using DBT and 2DDM in the intervention group, there will need to be a very small (0.45% to 0.9%) increase in lives saved by screening. In practice we expect a larger benefit than this.

Scattered Radiation Doses to Staff

The use of DBT as well as 2D imaging in the trial has the potential to increase the radiation dose to staff. Shielding of X-ray rooms is designed to ensure that radiation exposure outside the room is well below one third of the public radiation dose limit. In designing a mammography mobile for full-time 2D + DBT use, it is possible that additional shielding would be considered. However, as only one third of women imaged in any room during a year will receive DBT in addition to 2D imaging for this trial, we anticipate that additional shielding will not be necessary. However, this will be kept under review during the course of the trial and environmental radiation monitoring will be carried out to confirm that staff doses remain well within acceptable limits.

6.2 Ethics Reporting

There are no known SAEs anticipated which are specific to the trial intervention (DBT).

If there is an unexpected SAE at any site this will be reported to the National Trial Ethics Committee as part of the annual trial progress report.

If there is any breach of trial protocol at any site, this will be reported to the sponsor within seven days. The sponsor will be responsible for reporting the REC.

The Principle Investigator (PI) is responsible for:

- Assessing all AEs, ARs for severity, causality and expectedness.
- Reporting all SAEs within the agreed timelines to the CI (no later than 24 hours for KCH sponsored studies).
- Reporting all potential protocol violations and protocol / GCP breaches to the CI (no later than 24 hours for KCH sponsored studies).
- Promptly reporting all SUSARs, UADEs, potential protocol violations and protocol / GCP breaches as Trust serious untoward incidents via Datix (or local incident reporting method).
- Undertaking urgent safety measures and notifying the CI of the measures within the agreed timescales (no later than 24 hours for KCH sponsored studies).
- Proactively identifying and reporting all serious untoward incidents impacting on the delivery of research via Datix (or local incident reporting method).
- Contributing to any investigations undertaken by the Trust or sponsor and carrying out any relevant CAPA.

The members of the research team are responsible for:

- Identifying and reporting AEs, ARs and ADEs in the line with their responsibilities described in the trial delegation log.
- Proactively identifying and reporting of all serious untoward incidents impacting on the delivery of research via Datix (or local incident reporting method).
- Contributing to any investigations undertaken by the Trust or sponsor and carrying out any relevant CAPA.

The Chief Investigator is responsible for:

- Receipt and <u>initial assessment</u> of protocol and GCP breaches.
- Notifying sponsor of all potential serious breaches of GCP or the trial protocol within the agreed timescales (no later than 24 hours for KCH sponsored studies).
- Keeping detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
- Notifying sponsor of SAEs, SARs and SUSARs within the agreed timescales (no later than 24 hours for KCH sponsored studies).
- For medical devices studies notifying device manufactures of any SAEs, SADEs and UADEs no later than within 24 hours.
- Undertaking urgent safety measures and promptly notifying sponsor (no later than 24 hours for KCH sponsored studies).
- Promptly reporting all SUSARs, UADEs, potential protocol violations and protocol / GCP breaches as Trust serious untoward incidents via Datix (or local incident reporting method).
- Submitting the annual safety report to the sponsor, MHRA and REC.
- Proactively identifying and reporting all serious untoward incidents impacting on the delivery of research via Datix (or local incident reporting method).
- Contributing to any investigations undertaken by the Trust or sponsor and implementing any relevant CAPA.

The sponsor is responsible for:

- Receipt and assessment of all potential protocol and GCP breach notifications from the CI.
- Notifying REC of serious protocol and GCP breaches within the 7-day reporting timescale.
- Notifying REC of all protocol violations.
- Notifying REC of SUSARs within the 7-day reporting timescale for fatal and life-threatening events and 15-day timescale for events which are not fatal or life-threatening.
- Receiving notifications of urgent safety measures, undertaking urgent safety measures and promptly notifying all Investigators and REC of any findings that may affect the health of trial subjects.
- Investigating breaches and implementing corrective and preventative actions (CAPA).
- Submitting the annual safety report to the MHRA and REC.

The KCH R&I office carries out sponsor responsibilities for all KCH trials and research studies. The R&I office is responsible for coordinating investigations of all research incidents reported on Datix, in line with the procedure detailed in Appendix 5.

7. Trial Steering Committee

The trial steering committee will be formed of the CI, PIs, local service PIs, statistician and a representative of the Public and Patient involvement group. The committee will meet 2 x per annum and will be responsible for overseeing the trial, for collation and dissemination of results.

8. Ethics & Regulatory Approvals

The trial was granted a favourable ethical opinion on 09 February 2017 byLondon - Dulwich Research Ethics Committee. HRA approval was confirmed on 13 February 2017.

9. Data Handling

Confidentiality

1. Data source – Trial participant data will be stored on the national screening computer system (NBSS). Access to data on NBSS is password protected and is in accordance with the regulations and operating procedures within each of the trial sites. Access to trial participant data at the trial sites is limited to those involved in the direct clinical care of trial participants and the local trial data manager. The managers of the Central Trial Database at RSCH will need limited access in order to set up the anonymization process.
2. Time points for collection - Data on screening trial participants entered as routine at screen reading, assessment and following treatment
3. Screen readers, assessment team, local service data managers will collect the data
4. Data for trial participants will be downloaded and transferred to a central trial database which will be under the supervision of Dr Mark Halling-Brown at the Royal Surrey County Hospital, Guildford. Trial participants will be electronically labelled on the NBSS. A trial data set will be downloaded for each trial participant. Each trial participant will be given a unique trial number. Trial participant data will be held on an NHS computer and will be encrypted, password protected and pseudo-anonymised. Storage of trial participant data will be compliant with the Data Protection Act and with NHS Caldicott Guardian Regulations.

5. Participant trial data will be accessible at each of the screening sites by those responsible for the direct clinical care of the trial participants.
6. Anonymised data and images will be accessible by members of the trial steering group for data and image analysis.
7. Patient anonymity will be protected and maintained. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, the Research Governance Framework for Health & Social Care and Research Ethics Committee approval.
8. The CI is the custodian of the data.
9. No patient details to be transferred out of the EU
10. All patient data will be anonymised with regards to publications relating to the study.

Trial Participant Data Record

The source of trial participant data is the data which has been entered as part of routine clinical practice onto the NBSS. There is no additional data related to the trial which will be collected for the trial participants.

Archiving

An investigator site file will be held at each site and the relevant trial records will be archived at a secure site for 10 years.

Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

Clinical Governance Issues

Audit and Inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

- Project may be identified via the risk assessment process.
- An individual investigator or department may request an audit.
- A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.
- Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.
- Projects may be randomly selected for audit by an external organisation.
- Internal audits will be conducted by a sponsor's representative

Non-Compliance

The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action, including an on-site audit.

10. Finance and Publication Policy

Hologic Inc, Unit 2/Link 10/Napier Way, Crawley, RH10 9RA have agreed to provide funding for the trial subject to contract.

The trial committee have first publication rights of results from the trial.

No patient identifiable data will be used within the trial publications.

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

References

Alakhras, M. Bourne, R. Rickard, M. Ng, K.H. Pietrzyk, M. & Brennan, PC. (2013) Digital tomosynthesis: A new future for breast imaging? *Clinical Radiology 2013*. 68. p. 225-236.

Al Mousa, DS. Ryan, EA. Mello-Thoms, C. & Brennan, PC. (2014) What effect does mammographic breast density have on lesion detection in digital mammography? *Clinical Radiology 69* (2014) p. 333-341.

Bernardi, D. Caumo, F. Macaskill, P. Ciatto, S. Pellegrini, M. Brunelli, S. Tuttobene, P. Bricolo, P. Fanto, C. Valentini, M. Montemezzi, S. & Houssami, N. (2014) Effect of integrating 3D-mammography (digital breast tomosynthesis) with 2D-mammography on radiologists' true-positive and false –positive detection in a population breast screening trial. *European Journal of Cancer. 50*. (May 2014) p. 1232-1238.

Bernardi, D. Ciatto, S. Pellegrini, M. Anesi, V. Burton, S. Cauli, E. Depaoli, M. Larentis, L. Malesani, V. Targa, L. Baldo, P. & Houssami, N. (2012). Application of breast Tomosynthesis in screening: incremental effect on mammography acquisition and reading time. *British Journal of Radiology 85.* (December 2012) p. 1174-1178.

Bernardi, D. Ciatto, S. Pellegrini, M. Tuttobene, P. Fanto, C. Valentini, M. Michele, SD. Peterlongo, P. & Houssami, N. (2012) Prospective study of breast Tomosynthesis as a triage to assessment in screening. *Breast Cancer Research and Treatment 133.1.* (May 2012) p. 267-271.

Brandt, KR. Craig, DA. Hoskins, TL. Henrichsen, TL. Bendel, EC. Brandt, SR. & Mandrekar, J. (2013) Can digital breast Tomosynthesis replace conventional diagnostic mammography views for screening recalls without calcifications? A comparison study in a simulated clinical setting. *American Journal of Roentgenology 200.2* (Feb 2013) p. 291-298.

Centre for Cancer Prevention. (2014). Breast Screening Results from the NHSBSP 2012/2013 www.cancerscreening.nhs.uk/breast screen/uk-statistics-1213

Chen HH, Duffy SW, Tabar L, Day NE. (1997) Markov chain models for progression of breast cancer, part 1: tumour attributes and the preclinical screen-detectable phase. J. Epidemiol. Biostat. 2: 9-23

Ciatto, S. Houssami, N. Bernardi, D. Caumo, F. Pellegrini, M. Brunelli, S. Tuttobene, P. Bricolo, P. Fanto, C. Valentini, M. Montemezzi, S & Macaskill, P. (2013) Integration of 3D digital mammography with Tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *Lancet Oncology 2013.* 14. p. 583-589.

Day NE, Duffy SW. (1996) Trial design based on surrogate endpoints- application to comparison of different breast screening frequencies. J. Roy. Stat. Soc. (A) 159: 49-60

Destounis, S. Arieno, A. Morgan, R. & Elizabeth, W. (2014) Initial experience with combination digital breast Tomosynthesis plus full field digital mammography or full field digital mammography alone in the screening environment. *Journal of Clinical imaging science*. (Feb 2014)(4). p. 9

Destounis, SV. Morgan, R. & Arieno, A. (2015) Screening for dense breasts: digital breast Tomosynthesis. *American Journal of Roentgenology.* (February 2015). 202 (2). p. 261-4.

Duffy SW, Day NE, Tabar L, Chen HH, Smith TC. (1997) Markov models of breast tumour progression: some age-specific results. Monogr. Natl. Cancer Inst. 22: 93-97

Durand, MA. Haas, B. Yao, X. Geisel, JL. Raghu, M. Hooley, RJ, Horvath, LJ. & Philpotts, LE. (2015) Early clinical experience with digital breast Tomosynthesis for screening mammography. *Radiology 274.* (January 2015) (1). p. 85-92.

Evans, AJ. Breast Virtual Special issue. *Clinical Radiology 70 (2015) p681-683.*

Friedewald, SM. Rafferty, EA & Rose, SL. Durand, MA. Plecha, DM. Greenberg, JS. Hayes, MK. Copit, DS. Carlson, KL. Cink, TM. Barke, LD. Greer, LN. Miller, DP. & Conant, EF. (2014) Breast cancer screening using tomosynthesis in combination with digital mammography. *Journal of the American Medical Association 2014.* 311. (24) p. 2499-2507.

Gilbert, FJ. Tucker, L. Gillan, MGC. Willsher, P. Cooke, J. Duncan, KA. Michell, MJ. Dobson, HM. Lim, YY. Purushothaman, H. Strudley, C. Astley, SM. Morrish, O. Young, KC. & Duffy, SW. (2015) TOMMY trial: A comparison of TOMosynthesis with digital Mammography in the UK NHS Breast Screening Programme. *Health Technology Assessment 2015.* 19 (4).

Gilbert, FJ. Young, KC. Astley, SM. Whelehan, P. & Gillan, MGC. (2010) Digital Breast Tomosynthesis. *NHSBSP Publication September 2010.* 69.

Gilbert, FJ. Tucker, L. Young, KC. Digital Breast Tomosynthesis (DBT): A review of the evidence for use as a screening tool. *Clinical Radiology 71 (2016) p141-150.*

Greenberg, JS. Javitt, MC. Katzen, J. Michael, S. & Holland, AE. (2014) Clinical Performance Metrics of 3D Digital Breast Tomosynthesis Compared with 2D Digital Mammography for Breast Cancer Screening in Community Practice. *Women's Imaging 2014.* p. 687-693.

Gur, D. Zuley, M. Anello, MI. Rathfon, GY. Chough, DM. Ganott, MA. Hakim, CM. Wallace, L. Lu, A. & Bandos, A. (2012) Dose reduction in digital breast Tomosynthesis (DBT) screening using synthetically reconstructed projection images: an observer performance study. *Academic Radiology 19.2*. (Feb 2012) p. 166-171.

Haas, BM. Kalra, V. Geisel, J. Raghu, M. Durand, M & Philpotts, LE. (2013) Comparison of Tomosynthesis plus digital mammography and digital mammography alone for breast cancer screening. *Radiology 2013.* 269. p. 694-700.

Houssami, N & Skaane, P. (2013) Overview of the evidence on digital breast Tomosynthesis in breast cancer detection. *The Breast 2013.* 22. p. 101-108.

Houssami, N. & Zackrisson, S. (2013) Digital breast Tomosynthesis: the future of mammography screening or much ado about nothing? *Expert Reviews Med. Devices 2013.* 10. p. 583-585.

Houssami, N. Macaskill, P. Bernardi, D. Caumo, F. Pellegrini, M. Brunelli, S. Tuttobene, P. Bricolo, P. Fanto, C. Valentini, M. & Ciatto, S. (2014) Breast screening using 2D-mammography or integrating digital

breast Tomosynthesis (3D-mammography) for single-reading or double-reading – Evidence to guide future screening strategies. *European Journal of Cancer 2014.* p. 2-9.

Lee, CI. Cevik, M. Alagoz, & Tosteson, ANA. et al (2015) Comparative effectiveness of combined digital mammography and Tomosynthesis screening for women with dense breasts. *Radiology. 274.* (March 2015) (3). p. 772-780.

Lourenco, AP. Barry-Books, M. Baird, GL. Tuttle, A. & Mainiero, MB. (2015) Changes in recall type and patient treatment following implementation of screening digital breast tomosynthesis. *Radiology 274* (February 2015) (2). p. 337-342.

McCarthy, AM. Kontos, D. Synnestvedt, M. Tan, KS. Heitjan, DF. Schnall, M. & Conant, EF. (2014) Screening outcomes following implementation of digital breast Tomosynthesis in a general-population screening program. *Journal of the National Cancer Institute*. *106* (October 2013) (11).

Morel, J. Iqbal, A, Wasan, RK, Peacock, C. Evans, DR. Rahim, R. Goligher, J. & Michell, MJ. (2014). The accuracy of digital breast tomosynthesis compared with coned compression magnification mammography in the assessment of abnormalities found on mammography. *Clinical Radiology 69* (11) p. 1112- 6.

Michell, MJ. Iqbal, A. Wasan, RK. Evans, DR. Peacock, C. Lawinski, CP, Douiri, A. Wilson, R. & Whelehan, P. (2012) A comparison of the accuracy of film-screen mammography, full-field digital mammography, and digital breast Tomosynthesis. *Clinical Radiology 67*. (October 2012) (10). p. 976-981.

Offman, J. & Duffy, S. (2012) National Collation of Breast Interval cancer data. *NHS Cancer Screening Programmes.* (Dec 2012)
Rafferty, EA. Park, JM. Philpotts, LE. Poplack, SP. Sumkin, JH. Halpern, EF. & Niklason, LT. (2013) Assessing Radiologist Performance using Combined Digital Mammography and Breast Tomosynthesis compared with Digital Mammography Alone: Results of a Multicenter, Multireader Trial. *Radiology 2013.* 266 (1) p. 104-113.

Rose, SL. Tidwell, AL. Bujnoch, LJ. Kushwaha, AC. Nordmann, AS. & Sexton, JR. (2013) Implementation of breast Tomosynthesis in a routine screening practice: an observational study. *American Journal of Roentgenology 200.6.* p. 1401-1408.

Sechopoulos, I. (2013) A review of breast Tomosynthesis. Part I. The image acquisition process. *Medical Physics 2013*. 40

Sechopoulos, I. (2013). A review of breast Tomosynthesis. Part II. Image reconstruction, processing and analysis, and advanced applications. *Medical Physics 2013*. 40.

Skaane, P. Bandos, A. Gullien, R. Eben, E. Ekseth, U. Haakenaasen, U. Izadi, M. Jebsen, I. Jahr, G. Krager, M. & Hofvind, S. (2013) Prospective trial comparing full-field digital mammography (FFDM) versus combined FFDM and Tomosynthesis in a population-based screening using independent double reading with arbitration. *European Radiology 23.8*. (Aug 2013) p. 2061-2071.

Skaane, P. Bandos, AI. Eben, EB. Jebsen, IN. Krager, M. Haakenaasen, U. Ekseth, U. Izadi, M. Hofvind, S & Gullien, R. (2014) Two-view digital breast Tomosynthesis screening with synthetically reconstructed

projection images: comparison with digital breast Tomosynthesis with full-field digital mammographic images. *Radiology 2014.* 271. p. 655-663.

Skaane, P. Bandos, AI. Gullien, R. Eben, EB. Ekseth, U. Haakenaasen, U. et al. (2013) Comparison of digital mammography alone and digital mammography plus Tomosynthesis in a population-based screening program. *Radiology 2013*. 267. p. 47-56.

Wall BF, Haylock R, Jansen JTM, Hillier MC, Hart D, Scrimpton PC. HPA-CRCE-028: Radiation risks from medical X-ray examinations as a function of the age and sex of the patient. Health Protection Agency: Didcot, Oxfordshire (2011).

Warren LM, Dance DR, Young KC. Radiation risk of breast screening in the UK with digital mammography. Br J Radiol 2016 (In Press)

Yaffe, MJ. & Mainprize, JG. (2011) Risk of Radiation – induced Breast Cancer from Mammographic Screening, *Radiology 258* (1). p. 98-105.

Young KC, Oduko JM. Radiation doses received in the United Kingdom breast screening programme in 2010 to 2012. Br J Radiol 2016; 89: 20150831.

Zackrisson, S. Lang, K. Tingberg, A. & Andersson, I. (2014) Performance of one-view breast Tomosynthesis versus two-view mammography in breast cancer screening: first results from the Malmo breast screening trial. Presented at the European Congress of Radiology, Vienna, March 2014.

Appendix.

Study Sites

1. King's College Hospital
   Denmark Hill
   London
   SE5 9RS
   Dr Keshthra Satchithananda
   K.Satchithananda@nhs.net

2. The Jarvis Breast Centre
   Stoughton Road
   Guildford
   Surrey
   GU1 1LJ
   Dr Rita McAvinchey
   Rita.McAvinchey@nhs.net

3. Seacroft Hospital
   York Road
   Leeds
   West Yorkshire
   LS14 6UH
   Dr Nisha Sharma
   Nisha.Sharma2@nhs.uk

4. Avon Breast Screening Unit
   Bristol Breast Care Centre
   Beaufort House
   Southmead Hospital
   Westbury-on-Trym
   BS10 5NB
   Dr Alex Valencia
   alexandra.valencia@nbt.nhs.uk

5. St Bartholomew's Hospital
   Breast Screening Unit
   West Wing
   West Smithfield
   London, EC1A 7BE
   Dr Tamara Suaris
   Tamara.Suaris@bartshealth.nhs.uk

6. North London Breast Screening Service
   Deansbrook House
   Edgware Community Hospital
   Deansbrook Road
   Edgware
   Middlesex, HA8 9BA
   Dr Will Teh
   William.Teh@nhs.net

7. City, Sandwell and Walsall Breast Screening Service
   City Hospital
   Dudley Rd
   Birmingham, B18 7QH
   Dr Humaira Khan
   humairakhan@nhs.net