ODELIA

Open Consortium for Decentralized Medical Artificial Intelligence

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STUDY INITITIATION PACKAGE

Lead beneficiary	UKA
Author(s)	Daniel Truhn
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ODELIA

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EXECUTIVE SUMMARY

ODELIA has been registered as a clinical trial and the process of collecting the approval of the respective ethical committees has been started at every data-contributing site.

INTRODUCTION

In this deliverable we describe the current status of the registration of ODELIA as a whole as well as the current status of each data-providing partner's stance on the ethical agreement needed to conduct the study.

CLINICAL TRIAL REGISTRATION FOR ODELIA

ODELIA has been registered at ClinicalTrials.gov with the identifier NCT05698056.

APPROVAL OF LOCAL ETHICS COMMITTEES

- University Hospital Aachen (UKA): The study has been approved by the ethics committee.
- Vall d'Hebron Institute of Oncology (VIHO): All procedures for data collection, storage, and processing have been reviewed and approved by institutional ethics boards.
- University Hospital Zurich (USZ): The study has been approved by the ethics committee.
- University Medical Center Utrecht (UMC): Application has been submitted to the ethics committee and has been approved.
- University of Cambridge (CAM): Application has been submitted to the ethics committee and has been approved.
- MITERA: The study has been approved by the ethic's committee.
- Radboud university medical center (RUMC): Application has been submitted to the ethics committee and has been approved.
- RIBERA: Application has been submitted to the ethics committee and has been approved.

Note, that partners have not performed actions that might require approval or delivered data until approval by the local ethics committee had been granted.

ODELIA PROTOCOLS

We would like to clarify that there will not be a single, unified study protocol for this project. The examinations involved are breast MRI scans, and all data will be used retrospectively for training and validation purposes. In clinical practice, breast MRI examinations are conducted according to protocols established independently by each center, reflecting local practices and patient populations. Therefore, there is no universal standard protocol for breast MRI across all centers. This diversity in imaging protocols is representative of real-world clinical settings and is considered a

strength of our proposal, as it allows us to develop and validate models using heterogeneous data. The variation in data enhances the robustness and generalizability of our models, ensuring they are applicable across different clinical environments. Consequently, instead of a single study protocol, we are adhering to the local protocols of each participating center, each of which has obtained the necessary ethical approvals for the retrospective use of their data.

CONCLUSION

At the current point in time, we foresee no roadblocks to conduct ODELIA as planned. All necessary steps have been initiated.

ANNEXES

Site protocols are attached as annexes to this document. The following annexes are included in order:

- UKA
- CAM
- MHA
- RUMC
- RSH
- UMCU
- VHIO
- USZ

Study Protocol for Dynamic Contrast-Enhanced Breast MRI within the ODELIA Project

Introduction

This study protocol outlines the procedures for acquiring and processing dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) examinations of the breast, as part of the ODELIA project. The aim is to standardize data collection and imaging techniques to facilitate swarm learning and improve breast cancer detection and diagnosis across participating institutions.

Patient Enrollment and Clinical Assessment

Admission and Medical History

- **Patient Admission**: Female patients scheduled for breast MRI are admitted to the clinic.
- **Anamnesis**: A comprehensive medical history is taken, focusing on current and past health conditions.
- **Allergy and Contraindication Screening**:
    - Patients are queried about any known allergic reactions to contrast agents, particularly gadolinium-based compounds.
    - Contraindications for MRI, such as the presence of metallic implants, pacemakers, or claustrophobia, are assessed.
- **Family History**: Detailed information on familial breast cancer incidence is collected to evaluate genetic risk factors.
- **Clinical Information Gathering**: All relevant clinical data, including prior imaging studies and biopsy results, are documented.

Preparation for MRI Examination

Intravenous Access and Patient Briefing

- **Intravenous Catheter Placement**: An intravenous (IV) catheter is inserted into the patient's arm to facilitate contrast agent administration during the MRI examination.
- **Procedure Explanation**:

    - Patients receive a detailed explanation of the MRI procedure, including the purpose, duration, and any sensations they might experience.
    - Consent is obtained after ensuring the patient understands the procedure and has no further questions.

MRI Examination Protocol

Patient Positioning and Equipment Setup

- **Positioning**: Patients are placed in the prone position on the MRI table.
- **Breast Coil Application**:
    - A specialized breast four-element surface coil (Invivo, Orlando, FL, USA) is used.
    - An immobilization device (Noras, Würzburg, Germany) is employed to minimize motion artifacts by stabilizing the breasts in the craniocaudal direction.

MRI System Specifications

- **MRI System**: All imaging is performed using 1.5-Tesla MRI systems (Achieva; Philips Medical Systems, Best, The Netherlands).

Imaging Protocol

Dynamic Contrast-Enhanced Series

- **Sequence Type**: Axial bilateral two-dimensional multisection gradient-echo dynamic series.
- **Imaging Parameters**:
    - **Repetition Time (TR)**: 250 milliseconds.
    - **Echo Time (TE)**: 4.6 milliseconds.
    - **Flip Angle**: 90 degrees.
    - **Acquisition Matrix**: 512 × 512 pixels for high spatial resolution.
    - **Sensitivity Encoding (SENSE) Factor**: 2 to accelerate image acquisition and reduce scan time.
- **Contrast Agent Administration**:

    - A bolus injection of gadobutrol (Gadovist; Bayer, Germany) at a dose of 0.1 mmol per kilogram of body weight is administered via the IV catheter.
    - The dynamic series includes one pre-contrast and four post-contrast image acquisitions to assess the temporal enhancement patterns of breast tissue.
- **Timing**:
    - The pre-contrast images are acquired immediately before contrast agent injection.
    - Post-contrast images are acquired sequentially after contrast administration, maintaining consistent timing intervals to capture dynamic enhancement characteristics.

Additional Imaging

- **T2-Weighted Fast Spin-Echo Sequence**:
    - An axial T2-weighted sequence with identical anatomical coverage is performed.
    - This sequence aids in differentiating between cystic and solid lesions and provides additional anatomical details.
- **Parameters**:
    - The T2-weighted sequence shares the same spatial resolution and coverage as the dynamic series for image correlation.

Total Examination Time

- **Duration**: The entire MRI protocol is completed in less than 10 minutes, optimizing patient comfort and throughput.

Post-Examination Procedures

Patient Care and Results Discussion

- **Completion of MRI**:
    - After the imaging sequences are completed, patients are carefully removed from the MRI machine.

    - The IV catheter is removed, and the insertion site is checked for any signs of complications.

- **Consultation**:
    - Preliminary findings are discussed with the patient by a radiologist or attending physician, adhering to institutional policies regarding the communication of imaging results.

Data Collection and Processing for ODELIA

Data Extraction and Pseudonymization

- **Retrospective Data Extraction**:
    - MRI data are retrospectively extracted from the Picture Archiving and Communication System (PACS).
    - Associated clinical data, including biopsy results and histopathological confirmations of breast cancer, are collected.
- **Data Structuring**:
    - Clinical and imaging data are structured according to the ODELIA requirements to ensure consistency across sites.
- **Pseudonymization**:
    - All patient identifiers and sensitive information are removed or replaced with pseudonyms.
    - The pseudonymization process complies with the General Data Protection Regulation (GDPR) and institutional policies to protect patient privacy.

Data Storage and Swarm Learning Integration

- **Data Storage**:
    - Pseudonymized data are securely stored on dedicated servers designated for the ODELIA project.
- **Swarm Learning**:
    - The prepared datasets are utilized in swarm learning

Ethical Considerations

Patient Confidentiality and Data Protection

- **Compliance**:
    - The study adheres to all applicable ethical guidelines, including informed consent and the right to withdraw.
- **Regulatory Standards**:
    - Data handling practices conform to GDPR and other relevant regulations to ensure data security and patient confidentiality.

Study title: BrEast tissue response to Hyperoxic stimuli via blood Oxygenation Level-Dependent contrast change (BEHOLD)

Ethics Ref: 14/EE/0145

Date and Version No: 17 October 2017, version 4.0

Chief Investigator:	Prof Fiona J Gilbert Professor of Radiology, Head of Department, University of Cambridge
	Email: fjg28@cam.ac.uk Tel: 01223 336891
Investigators:	Dr Julia Carmona-Bozo PhD Student
	Dr Andrew J Patterson Clinical Scientist
	Dr Martin J Graves Consultant Clinical Scientist
	Dr Mary McLean MR Physicist
	Ms Gabrielle Baxter PhD Student
	Dr Tim D Fryer Head of PET Physics
	Dr Roido Manavaki PET Physicist
	Dr Nick Bird PET/CT Physics Lead, Clinical Scientist
	Dr John Buscombe Lead Consultant Nuclear Medicine and PET
	Dr Iosif Mendichovszky Honorary Speciality Registrar in Radiology
	Dr Ramona Woitek Breast Radiologist
	Dr Oshaani Abeyakoon Breast Radiologist
	Dr Turid Torheim Research Associate
	Mrs Sarah Hilborne Research Nurse
	Mrs Jackie Mason Research Nurse
	Mrs Ilse Patterson Lead R&D Radiographer
	Mrs Victoria Lupson Superintendent Research Radiographer
	Dr Elena Provenzano Breast Pathologist
	Prof Helena Earl Consultant Medical Oncologist
	Prof John Griffiths Head of Molecular Imaging Laboratory
	Prof Carlos Caldas Consultant Medical Oncologist
Sponsor:	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge

Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
4	4.0	17/10/2017	Dr Roido Manavaki	1. Modification to the inclusion criteria for participants in the patient arm of this study to allow inclusion of patients receiving neoadjuvant therapy as part of breast cancer management: The inclusion criteria for the patient cohort of this study have been modified to allow recruitment of patients with primary breast cancer, undergoing either primary surgery or neo-adjuvant therapy. This is to allow interrogation of a wider range of types, grades and molecular subtypes of breast cancer with BOLD/TOLD MRI and ^{18}F-FMISO PET. Furthermore, this will also allow assessment of whether these techniques can provide useful, potentially predictive information in the neoadjuvant setting. Participants receiving neoadjuvant therapy will be scanned at a single time-point during therapy and before the initiation of treatment. 2. Extension of the number of study patients (to n=70): In total, we would like to extend the study population to include 70 patients (currently 50) with primary invasive breast cancer who are scheduled for surgery and/or chemotherapy as part of their management. A sub-cohort of 40 patients (originally 20) are proposed to receive a

				combined PET/MR examination with ^{18}F-FMISO. 3. Inclusion of additional histological studies on diagnostic tissue specimens for comparison with MR and PET imaging information: Additional pathological information will be derived from tissue-based biomarkers, immunohistochemistry or genomic analysis on diagnostic specimens from the participants' scheduled surgery to correlate with PET and MRI biomarkers. The study will not generate additional tissue samples. 4. Modification in the data sharing plan outlined in the protocol: Data sets generated from this study may be made available without cost to internal researchers involved in basic, translational or clinical breast cancer research, and/or other local research studies in breast cancer. The data will be fully anonymised and made available upon request to the PI of the project. This will be conducted in compliance with the Data Protection Act 1998. 5. Changes in the study documentation: The participant information sheets and consent forms for the patient arm of the study have been updated to reflect changes in the inclusion criteria as outlined in the study protocol.
3	3.0	09/09/16	Dr Roido Manavaki	1. Combination of the separate MRI and ^{18}F-FMISO PET scans into a single ^{18}F-FMISO PET/MR examination: For patients

				participating in the ^{18}F-FMISO PET/CT sub-study, the ^{18}F-FMISO PET component of the PET/CT scan will be performed concurrently with the MR examination on PET/MR scanner. As simultaneous PET and MR acquisition can allow the examination of tumours under the same physiologic conditions, a single PET/MR examination will facilitate the effective comparison between MRI and established PET hypoxia markers. This approach also offers practical advantages for study participants by providing both scans within a single appointment and imaging session. 2. Inclusion of the low dose-CT component of the previous PET/CT examination as an optional scan: Subject to additional consent, the low-dose CT aspect of the replaced PET/CT examination may be performed in an additional imaging session for the assessment and cross-validation of PET/MR attenuation correction methods. There is no change to the total radiation exposure for patients participating in the sub-study. 3. Inclusion of The Wolfson Brain imaging Centre, University of Cambridge as an additional site for imaging examinations: The Wolfson Brain imaging Centre, University of Cambridge, Cambridge, UK has been included in the study protocol as a site for the performance of the MR and PET/MR imaging components of the study.

				4. Utilisation of pathology information for comparison with MR and PET imaging information: Histopathological analysis of surgical specimens will be conducted as per standard-of-care at Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust (CUHNHSFT). The study will utilise this information in order to validate MR and PET imaging biomarkers. The study will not generate any additional tissue samples. 5. Extension of the number of study patients (to n=50): To date, 24 breast cancer patients have been recruited into the MR component of the study. We would like to extend the cohort of patients participating in the study from 30 to 50, in order to facilitate the comparison between BOLD/TOLD MR and PET hypoxia biomarkers. This will also allow further optimisation of the BOLD/TOLD MR methods on the PET/MR scanner. 6. Changes in the list of study co-investigators: The list of study co-investigators has been updated to reflect the inclusion of the Wolfson Brain Imaging Centre, University of Cambridge as a site for imaging investigations. 7. Changes in study documentation: The participant information sheets and consent forms for both the healthy volunteer and patient arms of the study have been updated to reflect changes in the study protocol and the inclusion of the

				Wolfson Brain Imaging Centre, University of Cambridge as a site for imaging investigations.
2	2.0	20/10/14	Ms Tess Catherwood	One objective of this study is to investigate feasibility of quantitative T_1, and T_2* mapping in response to hyperoxic stimuli, however B_0 magnetic susceptibility effects present a problem for T_2*-weighted imaging at 3T. We would therefore like to amend the protocol to enable a sub-set of volunteer and patient research scans to be carried out at 1.5T. As detecting consistent oxygen-enhanced T_1 (TOLD) contrast changes in the breast has been challenging we would like also like to study oxygen-enhanced T_1 changes in organs with more established TOLD contrast response e.g. the spleen, in a second cohort of volunteers (n=30) in order to optimise and validate our technique. To facilitate these additional experiments, we would like to extend the study until October 2017.
1	1.2	8/10/14	Ms Tess Catherwood	To date, 9 volunteers have been scanned and a significant amount of work has been required to optimise the MRI protocol. We have noted variability in response between patients and we have noted that signal intensity response induced by the carbogen 'light' (2% CO_2) stimulus is slightly different to the response induced by carbogen

				(5% CO_2) as reported in the literature. For these reasons we would like to evaluate the test-retest repeatability of the BOLD sequence as well as performing a direct comparison between carbogen and carbogen 'light'.

1. Synopsis

Study Title	BrEast tissue response to Hyperoxic stimuli via blood Oxygenation Level-Dependent contrast change (BEHOLD)
Lay Title	Imaging oxygenation in breast cancer with novel MRI (magnetic resonance imaging) techniques
Internal ref. no.	
Study Design	Prospective, non-randomised, exploratory study in volunteers and patients
Study Participants	Volunteers and patients with pathologically confirmed breast cancer
Planned Sample Size	65 + 30 volunteers and 70 breast cancer patients
Follow-up duration	Patient cohort will be followed from their MR examination to their pathological reporting following surgery
Planned Study Period	3.5 years
Primary Objective	Establish the distribution of BOLD response to hyperoxic/hypercarbic stimuli at 3 Tesla in both normal parenchyma and in malignant tissue
Secondary Objectives	A. Evaluate if a novel 3D T_2-weighted sequence can detect a BOLD response following hyperoxic and hypercarbic stimuli using 3 Telsa MRI. Make direct comparison with a previously published 2D technique. B. Establish the optimal stimulus for detecting BOLD contrast in the breast C. Investigate the repeatability of BOLD contrast during hyperoxic/hypercarbic stimulus delivery at 3T D. Investigate feasibility of quantitative T_1, T_2 and T_2* mapping in healthy breast parenchyma in response to hyperoxic/hypercarbic stimuli at 1.5 and 3T. E. Investigate the relationship between BOLD/TOLD response to hyperoxic/hypercarbic stimuli and pharmacokinetic perfusion parameters F. Investigate the relationship between BOLD/TOLD response and (^{18}F-FMISO PET) hypoxia indices G. Investigate the relationship between BOLD/TOLD and PET hypoxia indices, histopathology results and genomic information H. Assess attenuation correction methodology for PET/MR imaging I. Investigate correlations between baseline BOLD/TOLD and PET hypoxia indices and radiological/pathological response in patients receiving neo-adjuvant therapy
Primary Endpoint	Infer if there is a statistically significant difference in BOLD response in healthy breast parenchyma versus malignant tissue
Secondary Endpoints	A. Assess the relative sensitivity of the signal intensity response using a novel 3D T_2-weighted BOLD sequence versus the previously published 2D technique.

	B. Report the BOLD response to different stimuli, specifically medical air versus carbogen and oxygen versus carbogen. Directly compare efficacy of 2% and 5% carbogen to induce BOLD response to interleaved stimulus design. C. Determine the test-retest coefficient of variation in the BOLD response to interleaved block stimulus design D. Report quantitative relaxometry (i.e. T_1, T_2 and T_2*) in healthy breast parenchyma in resting state and after the administration of hypercarbic/hyperoxic stimuli. E. Report the relationship between BOLD response to hyperoxic/hypercarbic stimuli and pharmacokinetic perfusion parameters F. Report the relationship between BOLD response and an established hypoxia marker (^{18}F-FMISO PET) on a subset of patients G. Correlate BOLD/TOLD and PET hypoxia biomarkers with pathology data derived from histopathological and genomic analysis of diagnostic biopsies/surgical specimens H. Assess MR-based attenuation correction methods for PET/MR imaging I. Correlate baseline BOLD/TOLD and PET hypoxia indices and radiological/pathological response in patients receiving neo-adjuvant therapy
Intervention (s)	Volunteers will undergo a single MR examination lasting ~40 min. Patients will undergo a single MR examination lasting ~1 hour. For the patient cohort, a BOLD research sequence will be appended to an existing DCE-MRI protocol which includes B_1 mapping, T_1 mapping and a dynamic contrast enhanced acquisition. Medical gases (oxygen, carbogen and medical air) will be delivered during imaging using an in-house gas delivery system. Up to 40 patients will also undergo a combined ^{18}F-FMISO PET/MR examination. Subject to additional consent, patients participating in the FMISO PET/MR examination may undergo an additional low-dose CT scan for PET attenuation correction purposes. Up to 12 subjects will undergo two MR scans (within 48 hours).

2. Background and Rationale

2.1 Breast cancer and the role of imaging

Breast cancer is the most prevalent female cancer worldwide, accounting for 14% of cancer deaths and 23% of the total new cancer cases in 2008[1]. Magnetic resonance imaging (MRI) techniques are being increasingly used for breast cancer detection, diagnosis and staging as they provide improved sensitivity and specificity compared to conventional mammography[2]. Dynamic contrast-enhanced MRI (DCE-MRI) is the current standard for breast MR imaging and provides information on tumour perfusion and permeability. Given the common use of DCE-MRI in breast cancer patients, the development of complementary non-invasive techniques to characterise tumour oxygenation remains attractive.

Blood (BOLD) and tissue (TOLD) oxygenation level-dependent MRI is sensitive to vasoreactivity and tissue oxygenation, due to the paramagnetic effects of deoxyhaemoglobin and dissolved oxygen. Measuring signal intensity changes in response to either hyperoxic and/or hypercarbic respiratory challenges has the potential to assess dynamic tumour oxygenation changes, vasoreactivity, vessel maturity and function[3]. Hypoxia is a feature of most solid tumours, including breast cancer[4], and is associated with angiogenesis, local recurrence and metastasis, as well as therapy resistance and poor patient outcome[5]. The precise relationship between tissue hypoxia and the dynamic response to hyperoxic and hypercarbic stimuli is complex, but some general trends have emerged[6].

2.2 Blood (BOLD) and tissue (TOLD) oxygenation level-dependent MRI

An array of studies have reported dynamic signal intensity changes as a result of hyperoxic and/or hypercarbic stimuli[3,7–21]. Dynamic changes in quantitative MR relaxometry have been investigated and relate to tissue oxygenation ($R_1 = 1/T_1$) and vascular deoxyhemoglobin ($R_2^* = 1/T_2^*$). Breathing a hyperoxic stimulus induces variations in blood and tissue oxygenation via two mechanisms as additional oxygen molecules (i) saturate the deoxygenated haemoglobin and (ii) dissolve in blood plasma and tissue fluids. Deoxyhaemoglobin is paramagnetic and a drop in deoxyhaemoglobin fraction of blood causes the transverse relaxation rate (R_2^*) to decrease, acting as an endogenous blood oxygenation level-dependent (BOLD) contrast agent. The effects of various hyperoxic stimuli on R_2^* have been evaluated in normal tissue and various tumour types[19], including head-and-neck[14,18], breast[9,13,16], cervical[10] and prostate cancer[7,11], where blood-volume corrected R_2^* has been shown to be a reliable marker of tissue hypoxia. To a minor degree, increased concentration of dissolved oxygen also causes a small increase in R_2^*, however this is generally not detectable due to the more dominant BOLD effect.

Supraphysiological levels of paramagnetic oxygen molecules dissolved in plasma and tissue fluid shortens tissue longitudinal relaxation time (T_1), which provides a mechanism for monitoring oxygen delivery to tissues distinct from the BOLD effect. In theory, elevated levels of dissolved oxygen persist to the arteriolar vessels to increase tissue pO_2, providing tissue oxygenation level-dependent (TOLD) contrast. This effect has been exploited to measure T_1 changes in normal tissue[15,20,22] and tumours[21].

When presented with a hyperoxic stimulus, normal perfused tissue exhibits a subtle decrease in R_2^*, consistent with a small drop in deoxyhaemoglobin[15]. The extent of this decrease is regulated by the

vasoconstrictive capillary response to the hyperoxic stimulus. In tumour tissue, angiogenesis causes proliferation of immature vasculature characterised by structural and functional abnormalities. A substantial decrease in R_2* has been observed in perfused tumours, which signifies high oxygen saturation per volume element, as a result of poor vasoconstriction. Little to no R_2* response within tumours has also been reported; this may indicate the absence of any oxygen delivery, signifying a region of severe hypoxia. R_1 increases in normal tissue in response to a hyperoxic stimulus, consistent with a six-fold increase in dissolved oxygen levels. Well perfused tumour regions with oxygenated haemoglobin should exhibit similar increases in R_1 – a lack of R_1 response may be indicative of low baseline oxygenation, due to the high affinity of oxygen for haemoglobin.

However, the precise mechanism of R_1 and R_2* modulation by hyperoxic and hypercarbic stimuli is unclear – many aspects of physiology including vessel architecture, blood flow and volume effects, oxygen diffusion, metabolism and tissue necrosis may be involved. This is reflected by some confounding evidence in the literature regarding R_2* response following oxygen challenge: O'Connor *et al.* reported no significant change in R_2* following inhalation of 100% oxygen[15], however other studies have demonstrated a measurable BOLD response[9,10,13]. A more consistent change in R_2* with carbogen breathing has been reported. Breathing 100% oxygen increases partial pressure of oxygen in the vascular system, leading to tissue oxygenation (decreased R_2*); however, hyperoxia also causes a consequential decrease in CO_2, leading to vasoconstriction and a subsequent decrease in tissue oxygenation. Trade-offs between these two competing mechanisms may lead to variability between subjects due to biodiversity. Carbogen (typically 5% CO_2 and 95% O_2) increases oxygen delivery by providing a hyperoxic stimulus, whilst maintaining vasodilation. In general, oxygen is well-tolerated but produces more variable BOLD contrast, whereas carbogen is a more robust stimulus but some subjects find it difficult to breathe. Decreased concentrations of carbon dioxide are much better tolerated by patients and have been shown to be equally effective at increasing tissue oxygenation[23,24]: this gas mixture combination (2% CO_2 and 98% O_2) has been coined 'carbogen light'. Improved understanding of the physiological response in healthy breast parenchyma at 3T following hyperoxic and hypercarbic stimuli also remains essential.

BOLD and DCE-MRI are both well recognised approaches for assessment of vessel maturation and function, however few studies to date have investigated sequential BOLD and DCE in individual tumours. Both approaches are sensitive to some characteristics, such as vascular flow and volume, but are uniquely sensitive to other properties such as perfusion (DCE) and oxygenation (BOLD). Jiang *et al.* found no relationship between BOLD and DCE-MRI, however they employed semi-quantitative MRI analyses instead of pharmacokinetic modelling[25]. Baudelet *et al.* analysed BOLD and DCE and found weak correlations between their corresponding derived parameters[26].

2.3 BOLD contrast in the breast

To date, there have been several noteworthy reports of BOLD contrast in response to hyperoxic and/or hypercarbic stimuli in breast cancer patients. Taylor *et al.* studied a broad range of tumours including a single breast adenocarcinoma and found a 62% increase in T_2*-weighted signal accompanying carbogen challenge at 1.9T[19]. In a preliminary case report, Fischer *et al*. reported a 15% increase in T_2*-weighted relative signal intensity in a breast tumour at 1.5T accompanying oxygen challenge[9]. A recent pilot study (n=7) by Jiang *et al.,* measuring the BOLD response to oxygen at 1.5T prior to neoadjuvant

chemotherapy, found that the BOLD response was significantly greater ($P < 0.001$) in patients who ultimately exhibited a complete pathological response (average ΔSI = 12%) versus partial response or stable disease (<2% ΔSI)[13]. This tentative data supports the underlying theory that hypoxic tumours with poor vasculature and function also exhibit little to no BOLD response and suggests that this non-invasive technique may be a valuable adjunct to DCE-MRI to predict response to chemotherapy. Widely differing enhancement patterns between DCE and BOLD images were observed at the same tumour location, indicating BOLD data may provide additional tissue oxygenation information not explained by perfusion alone[13].

A recent study by Rakow-Penner *et al.* represents the first major effort to develop a robust technique to measure BOLD contrast in the human breast at 3T[16]. Gradient echo and spin echo based pulse sequences were tested using a multiple interleaved gas stimulus design. The experiments were conducted on 15 normal volunteers and in three breast cancer patients. Most previous studies employed a 2D gradient-recalled-echo (GRE) sequence to measure BOLD response using either a relative or quantitative T_2* change. Rakow-Penner *et al.* reported obscure and inconsistent BOLD contrast maps with GRE imaging at 3T, due to the adversely heterogeneous B_0 field created by the breast geometry[16]. Instead a single-shot fast spin echo (SSFSE) sequence was used to detect changes in T_2 relaxivity, which provided more robust and consistent data.

Other interesting developments in this area include Liu *et al.'s* study, which demonstrated a correlation between mean baseline R_2* values and the level of hypoxia inducible factor-1α (HIF-1α), a molecule shown to be responsible for orchestrating the aggressive behaviour of cancer cells and their resistance to therapy[27].

2.4 BOLD MRI and ^{18}F-FMISO PET for assessment of tissue hypoxia

Hypoxia is an important biomarker for tumour progression and response to therapy. Various techniques have been developed for the assessment of tissue hypoxia. Direct assessment of hypoxia *in vivo* typically involves the utilisation of polarographic oxygen electrodes, which can provide absolute measurements of tissue oxygenation at the sampling location. However, this procedure is technically demanding, invasive, inconvenient, highly susceptible to sampling errors, and impractical in the clinical setting. BOLD MRI may be able to inform on tissue hypoxia, based on the assumption that the oxygenation of haemoglobin is proportional to blood arterial pO_2, which is in equilibrium with oxygenation of surrounding tissues.

The most widely employed, non-invasive method for the measurement of hypoxia *in vivo* involves the use of positron emission tomography (PET) and radiohalogenated derivatives of the 2-nitroimidazoles. From this family of compounds, ^{18}F-fluoromisonidazole (^{18}F-FMISO) constitutes the prototype PET hypoxia tracer, and has been extensively utilised in the study of hypoxia in oncology[28]. In a similar manner to all nitroimidazole analogues, ^{18}F-FMISO undergoes intracellular reduction and becomes selectively trapped in hypoxic regions (pO_2<10mmHg) by covalently binding to cellular molecules at rates that are inversely proportional to intracellular oxygen concentration[29–31]. Given that ^{18}F-FMISO PET can provide a more specific biomarker of hypoxia in tumours, initial studies in humans[32] and the pre-clinical setting reporting on the comparison of imaging results obtained from BOLD-MRI and ^{18}F-

FMISO PET experiments have demonstrated good correlations between the two techniques[33,34], thus, highlighting the role of BOLD MRI as a promising tool for the non-invasive imaging of tumour hypoxia.

2.5 Development of BOLD and TOLD breast MRI at 3T

There is currently no consensus on the optimal pulse sequence or stimulus design for detecting BOLD and TOLD contrast in breast tissue. Highlighted areas for development include imaging at higher field strengths, 3D acquisition strategies and measurement of quantitative parameters.

Most studies investigating BOLD contrast change in response to hyperoxic and/or hypercarbic stimuli have been conducted at 1.5T. 3T MRI produces a theoretical doubling of signal to noise ratio, compared to 1.5T, which can be offset to achieve higher spatial or temporal resolution. 3T also increases the 'BOLD effect', producing a greater change in T_2* for the proportional change in deoxyhaemoglobin. However, measuring blood oxygenation effects at 3T presents unique technical challenges for breast imaging, including RF transmit and static magnetic field inhomogeneity. On-going work to support DCE-MRI breast studies has evaluated corrective techniques to help overcome these challenges.

A limitation of the previous 3T implementation, proposed by Rakow-Penner *et al.*, is that it only assesses BOLD response at a single 2D slice location, and the positioning of an optimal slice location may be difficult to identify pre-contrast administration. 3D techniques would allow better characterisation of the spatial relationship between vasoconstriction and function. 3D variable refocusing flip angle FSE has been proposed to enable the prescription of longer echo train lengths while mitigating T_2 blurring artefact[35]. This approach attempts to maintain the amplitude of the magnetisation by varying the refocusing flip angle over the duration of the echo train. This in effect allows for more k-space coverage per repetition time. Parallel acceleration can also be applied independently. Initial optimisation experiments have shown that these approaches can be combined to allow the acquisition of dynamic 3D T_2-weighted images with a temporal resolution of ~13 s.

The majority of studies investigating BOLD-MRI in the breast have measured changes in signal intensity in T_2*-weighted images with respect to vasoactive challenges. These simple contrast changes have been temporally correlated with pO_2[6,36], however analysis of quantitative parameters should provide more robust data. T_2*-weighted signal response may be influenced by variation in vascular inflow, denoted as flow and oxygenation dependent (FLOOD) contrast by Howe *et al*[37]. Quantitative measures of R_2* are independent of flow effects and allow comparison of values independent of TE, TR and signal intensity. Changes in R_1 in response to a hyperoxic stimulus have not yet been evaluated in the breast. The proposed study plans to report relaxometry in healthy breast parenchyma and in malignant tissue in resting state and following hyperoxic/hypercarbic stimuli.

This study will therefore evaluate optimal techniques for measuring BOLD and TOLD response at 1.5T and 3T in normal volunteers and determine the clinical feasibility of this technique for depicting tumour oxygenation in breast cancer, comparing BOLD MRI, DCE-MRI and ^{18}F-FMISO PET.

3. Objectives

3.1 Primary Objective

The principal objective of this pilot study is to investigate the ability of BOLD MRI to measure dynamic tumour oxygenation changes, vasoreactivity, vessel maturity and function in breast cancer patients (n=50 patients).

Hypothesis: BOLD research sequences measuring response to hyperoxic/hypercarbic stimuli can be used to assess oxygenation of breast tumours non-invasively.

3.2 Secondary Objectives

A. Evaluate if a 3D T_2-weighted sequence can detect a BOLD response following hyperoxic/hypercarbic stimuli and make direct comparison with a previously published 2D technique[16] (n=15 volunteers)

B. Establish the optimal stimuli for detecting BOLD contrast in the breast, comparing carbogen vs. oxygen and carbogen vs. medical air, and making a direct comparison between different levels of CO_2 in carbogen (2% vs. 5%) (n=25 volunteers)

C. Investigate the repeatability of BOLD contrast during hyperoxic/hypercarbic stimulus delivery at 3T (n=12 volunteers/patients)

D. Investigate quantitative relaxometry at 1.5T and 3T in healthy breast parenchyma in response to hyperoxic/hypercarbic stimuli (n=15 volunteers)

E. Investigate the relationship between BOLD response to hyperoxic/hypercarbic stimuli and pharmacokinetic perfusion parameters (n= 70 patients)

F. Compare BOLD/TOLD response in malignant tissue with a direct marker of tissue hypoxia ^{18}F-FMISO PET in a sub-sample of patients (n= 40 patients)

J. Compare BOLD/TOLD response and ^{18}F-FMISO PET hypoxia indices, and investigate the relationship between image-based hypoxia indices, histopathology results and genomic information from diagnostic biopsies or surgical specimens

G. Assess attenuation correction methodology for PET/MR imaging

H. Investigate correlations between baseline BOLD/TOLD and PET hypoxia indices and radiological/pathological response in patients receiving neo-adjuvant therapy.

4. Study Design

4.1 Summary of study design

This pilot study is a prospective, non-randomised, exploratory study in volunteers and patients.

Volunteers will be scheduled to undergo an MR examination at the MRIS unit at Addenbrooke's hospital or the Wolfson Brain Imaging Centre lasting ~40 minutes. A sub-set of volunteers will be asked to undergo a second MR examination in order to assess repeatability of the technique.

Patients will undergo a standard MR or PET/MR examination before their surgery. A BOLD research sequence (~20 minutes) will be appended to the MR examination. The entire examination should take ~1 hour. A subset of patients will also undergo a combined ^{18}F-FMISO PET/MR examination subject to obtaining additional consent.

The study is expected to take 3.5 years and run from May 2014 to October 2017. At the conclusion of the study, participants will be informed in writing regarding the scientific outcomes.

4.2 Primary and secondary endpoints/outcome measures

4.2.1 Primary outcome measure

Establish the distribution of BOLD response at 3 Tesla in both normal parenchyma and in malignant tissue; infer if there is a statistically significant difference in BOLD response in healthy breast parenchyma versus malignant tissue.

4.2.2 Secondary outcome measures

A. Report the relative sensitivity of a novel 3D BOLD sequence appropriate for 3T breast imaging and make direct comparison with the previously published 2D SSFSE technique[16] (Rakow-Penner *et al.*)

B. Establish the sensitivities of the following stimuli for detecting BOLD response: medical air vs. carbogen and oxygen vs. carbogen. Compare the magnitude of BOLD response induced by 2% and 5% carbogen.

C. Report the test-retest coefficient of variation in the BOLD response to interleaved block stimulus design

D. Report the distributions of quantitative relaxometry (T_1, T_2 and T_2*) pre- and post-hyperoxic/hypercarbic stimuli in healthy breast parenchyma.

E. Report the relationship between pharmacokinetic perfusion parameters and BOLD response in malignant tissue

F. Report the relationship between ^{18}F-FMISO PET and BOLD response

G. Correlate baseline BOLD/TOLD and PET hypoxia indices and radiological/pathological response in patients receiving neo-adjuvant therapy.

4.3 Study Participants

4.3.1 Overall Description of Study Participants

Participants with pathologically confirmed primary breast cancer, and healthy female adults, aged 18 years or above

4.3.2 Inclusion Criteria for volunteer cohort

- Participant is willing and able to give informed consent for participation in the study
- Female, aged 18 years or above

Inclusion Criteria for additional volunteer cohort to validate TOLD contrast technique

- Participant is willing and able to give informed consent for participation in the study
- Male or female, aged 18 years or above

4.3.3 Additional inclusion criteria for patient cohort

- Pathologically confirmed primary breast cancer
- Planned treatment is primary surgery or neoadjuvant therapy
- Tumour >1cm diameter

4.3.4 Exclusion Criteria

- Pregnant
- Implants known to be contraindicated at 3 Tesla
- Patients under treatment for chronic obstructive pulmonary disease (COPD)
- Vulnerable patient groups
- Unable to provide informed consent
- Medically unstable
- History of serious breast trauma within past 3 months
- Undergoing MRI for assessment of the integrity of breast implants

4.3.5 Additional exclusion criteria for patient cohort

- History of kidney disease or known allergic reaction to Gd contrast agent
- Has undergone chemotherapy or hormonal therapy for breast cancer in previous 12 months
- Had previous surgery or radiotherapy for cancer to the ipsilateral breast or previous surgery to the ipsilateral breast within the past 4 months for benign breast disease

4.4 Study Procedures

4.4.1 Informed Consent

An advertisement poster will be placed outside the department to recruit volunteers into the study.

Women suitable for the patient arm of this study will be identified at the breast multi-disciplinary team meeting. Patients with breast cancer satisfying the inclusion and exclusion criteria for the study (Sections 4.3.3-4.3.5), will be approached in the clinic after they have received their core biopsy results.

All potential participants will be provided with a participant information sheet and a consent form. The plan and reason for the study will be explained and participants will be given the opportunity to ask questions. Participants will be given a minimum of 24 hours to decide whether or not to take part (in practice, participants will be given several days to decide) before consent is taken by the principal investigator or a suitably qualified, delegated member of the clinical care team (patients) or research team (volunteers). The investigators will also obtain permission from patients with regards to informing their general practitioner about their study involvement and communicating any important medical findings found during the study.

4.4.2 Study Assessments

After voluntary, informed consent has been taken; participants will be scheduled to undergo an MR examination at the MRIS unit at Addenbrooke's Hospital, Cambridge or at the Wolfson Brain Imaging Centre, University of Cambridge (directly adjacent to Addenbrooke's Hospital). Examinations will be conducted using a 1.5T MRI system (MR450, GE Healthcare) or a 3T MRI system (MR750, GE Healthcare or Signa PET/MR, GE Healthcare) with a suitable surface coil. A careful explanation will be given with regards to what to expect when breathing carbogen to maximise participant compliance.

Scout images will be acquired whilst the participant is breathing room air. Medical grade oxygen, 'carbogen-light' (2% CO_2 and 98% O_2) and/or carbogen (5% CO_2 and 95% O_2) and medical air will be administered through a facemask during BOLD imaging. An in-house gas delivery system will be used to enable interleaved delivery of the medical gases. A respiratory belt and a photoplethysmograph will be placed on each subject to record respiratory function and cardiac rate. End tidal CO_2 will be recorded via a sample line to demonstrate participant compliance with the protocol. An intravenous catheter will be inserted into an arm vein for contrast agent administration (patient cohort only).

Participants may be asked if they would agree to come back for a second scan within 48 hours in order to assess repeatability of the technique.

Participants in the patient arm of this study, scheduled for neoadjuvant therapy that have agreed to the combined PET/MR examination part of this protocol, will undertake *one* such examination *at baseline* and before the initiation of any therapy regime as part of their treatment plan.

4.4.2.1 Volunteer study

T_1- and T_2-weighted standard anatomical scans will be undertaken while the subject is breathing medical air. In 15 volunteers, BOLD response to interleaved oxygen and carbogen will be imaged using a multi-phase 3D T_2-weighted sequence. A multi-phase 2D SSFSE sequence will be applied to replicate

the results reported by Rakow-Penner *et al*.[16] Medical air and carbogen will be interleaved to investigate the optimal stimulus design in a further 15 volunteers.

In up to 15 volunteers, quantitative T_1 and T_2 mapping will be explored. Optimised 3D spoiled gradient echo or 2D inversion recovery-based images will be acquired to estimate tissue R_1 relaxation rate. A series of T_2-weighted images will be acquired to enable calculation of tissue R_2. Measurements of R_1 and R_2 will be repeated while breathing oxygen and carbogen, allowing for a short transition period.

Volunteer study to validate TOLD contrast technique

In up to 30 volunteers, quantitative oxygen-enhanced T1 mapping will be explored in the spleen and other abdominal organs using either a 3D spoiled gradient echo variable flip angle method or a 2D inversion recovery-based method to estimate tissue R_1 relaxation changes. Medical grade oxygen or carbogen will be administered.

The optimized technique will then be applied in the breast volunteer and patient cohorts.

4.4.2.2 Patient study

After voluntary, informed consent has been taken; 30 patients will undergo an MR examination. This research examination will replace the routine clinical breast MR examination, if an MRI scan is part of the management plan. The research examination will last approximately 20 minutes longer than a standard breast MRI examination, which lasts approximately 35 minutes.

Patients will receive a DCE-MRI protocol to investigate the relationship between BOLD and pharmacokinetic parameters and to allow depiction of the spatial extent of the tumour. B_1 mapping will be undertaken using the Bloch-Siegert method to perform a spatial mapping of the B_1+ field to spatially correct the flip angles. Baseline T_1 relaxation time will be determined by using variable flip angle approach. Patients will receive a controlled administration of 0.1 mmol/kg of Gd based contrast. An optimised BOLD imaging protocol with oxygen and/or carbogen will be appended to the DCE protocol.

A subset of up to 20 patients will undergo a combined PET/MRI examination with ^{18}F-FMISO, so as to assess the association between ^{18}F-FMISO accumulation, an indicator of hypoxia and signal changes in BOLD-MRI with oxygen and/or carbogen inhalation, a potential hypoxia marker.

The PET/MR scan will be performed on a GE Signa PET/MR scanner at the Wolfson Brain Imaging Centre, University of Cambridge, Cambridge. Participants are not required to fast prior to the PET/MR examination. All subjects will receive 300 MBq of ^{18}F-FMISO intravenously followed by a 120 min uptake period. The interval between tracer injection and acquisition is necessary to enhance the hypoxic-to-normoxic tissue differentiation in PET images, as well as to allow for the free ^{18}F-FMISO concentration in tissue to equilibrate with the blood (required for the determination of the influx rate constant K_i via Patlak plot analysis). Participants will undergo a 60 min dynamic PET scan acquired in list-mode, with MR imaging performed with PET acquisition. The scan will involve a single bed position covering the entire breast area, with the tumour centred in the axial FOV. Venous blood samples (<6 ml each) will be obtained at three time points during the ^{18}F-FMISO PET scan: at the start of PET acquisition (120 min post injection); 30 min after the start of PET acquisition (150 minutes post

injection) and at the end of PET acquisition (180 minutes post injection). The venous blood samples will be employed for scaling a population-based arterial input function derived from existing data, and thus allow estimation of K_i (influx rate of ^{18}F-FMISO from plasma into the trapped compartment), which is a more specific measure of hypoxia. Images will be reconstructed using a 3D time-of-flight (TOF) iterative reconstruction algorithm, as implemented on the scanner, with corrections applied for attenuation, scatter, random events, dead time, normalisation, sensitivity and isotope decay.

Subject to additional consent, patients participating in the PET/MR examination may undertake a low-dose CT scan of the breast area at the PET/CT Unit, Addenbrooke's Hospital, Cambridge for PET attenuation correction purposes and to assess attenuation correction methodology for PET/MR imaging. The total duration of the CT imaging session will be ~10 minutes.

The estimated effective dose to women from ^{18}F-FMISO is 0.014 mSv/MBq[38], giving a dose of 4.2 mSv for an in300 MBq. The effective dose for the CT imaging aspect of the study is 0.9 mSv. The estimated total radiation exposure from the PET and CT scans is 5.1 mSv.

4.5 Definition of End of Study

The end of study is the date of the last MRI, PET/MR or CT scan of the last participant.

5. Interventions

No interventions will be performed beyond standard of care.

6. Safety Reporting

6.1 Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.2 Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form (see NRES website).

7. Statistics

7.1 The number of participants

This pilot study aims to recruit 70 patients with primary breast cancer and image them prior to surgery or initiation of treatment. For the purpose of this pilot study, with the primary objective of assessing the clinical feasibility of BOLD MRI, insufficient prior knowledge is available to perform a formal sample size calculation. Up to 40 patients will undergo PET with ^{18}F-FMISO in addition to MR examination to investigate the relationship between BOLD response and tumour hypoxia. These defined sample sizes have been determined based on pragmatic considerations of the anticipated recruitment rates.

In addition, this study will aim to recruit a further 65 healthy female adults. This will allow optimisation of BOLD imaging in the breast, including comparison of 2D/3D and quantitative/non-quantitative techniques, stimulus optimisation, and exploration of different contrast mechanisms and assessment of repeatability.

A further 30 healthy adults will be recruited for the purposes of validating and optimising a technique for detecting oxygen-enhanced T_1 changes.

7.2 Analysis of Endpoints

BOLD signal intensity changes will be cross-correlated with a sinusoidal model (approximating the haemodynamic response function of the stimulus in breast tissue) to generate correlation coefficient maps and quantify phase lag by extending the methodology proposed by Rakow-Penner *et al*. to 3D[16]. In addition, a novel approach to generate statistical activation maps based on the randomisation test originally proposed by Holmes *et al.* will be investigated[39].

The primary statistical hypothesis is to investigate if there is a statistically significant difference in BOLD signal intensity response in normal breast parenchyma versus malignant tissue. We will formally evaluate if the distributions meet normality assumptions using a Shapiro-Wilks W test. Appropriate univariate statistics will then be performed (Student's T-test or Mann-Whitney U respectively), dependent on the normality assumptions.

DCE-MRI pharmacokinetic modelling will be undertaken and gadolinium concentration over time will be modelled after quantifying baseline longitudinal relaxation (T_1 mapping) and correcting for RF transmit inhomogeneity (B_1 mapping). The relationship between BOLD and DCE metrics will be investigated by performing formal statistical analyses to assess the normality assumptions of each

respective distribution. Appropriate univariate statistics will then be performed to express the relationship between the various imaging markers.

Other secondary aims of the project include optimising BOLD contrast in the breast at 3T. 2D and 3D approaches will be compared. Magnitude and variability of BOLD response will be compared between stimuli. Inter-subject test-retest coefficient of variation will be calculated in subjects undergoing two MR scans to assess the reproducibility of the technique.

PET image data analysis: In order to reduce the impact of patient motion during PET acquisition, the 12 frames comprising the dynamic PET image series will be non-rigidly registered to the first frame. The last three of the registered frames (165-180 min post injection) will be utilised for the generation of SUV and T/B-maps for the determination of ^{18}F-FMISO uptake as standardised uptake values (SUV) and tumour-to-blood ratios (T/B) respectively. The hypoxic fractional volume (HFV) – defined as the number of pixels in the tumour volume that have crossed a T/B threshold of 1.2[40] (indicative of hypoxia) multiplied by the volume of the voxel will also be calculated from the ^{18}F-FMISO T/B-maps. Given that increased tracer uptake, as quantified by SUV or T/B ratios, may represent high tracer delivery to a region of interest, rather than tracer trapping under hypoxic conditions, the influx rate of ^{18}F-FMISO into the trapped tissue compartment (K_i) in addition to SUV and T/B will also be determined, as a more specific measure of tumour hypoxia. K_i maps will be produced on the basis of all of the frames in the registered dynamic series and the population-based arterial plasma input function, scaled by the venous blood samples obtained during PET acquisition, utilising Patlak plot analysis.

Comparison between BOLD-MRI and ^{18}F-FMISO PET: A comparison study between ^{18}F-FMISO-PET and BOLD MRI will be conducted, so as to assess the relationship between signal changes in BOLD-MRI and ^{18}F-FMISO accumulation indices (SUV, T/B, HFV, K_i). To facilitate comparison between the two techniques, the PET parameter maps will be co-registered with the MR images. Regions of interest (ROI) will be drawn across the entire tumour on several slices on the DCE-MR images by a radiologist, and will then be superimposed onto the PET and BOLD maps, so as to obtain regional values for the SUV, T/B, K_i, HFV indices from the PET and signal intensity changes from BOLD-MRI maps. The relationship between BOLD and ^{18}F-FMISO-PET parameters will be assessed using multi-variate regression analysis.

Comparison between BOLD-MRI and ^{18}F-FMISO PET hypoxia biomarkers and histopathology: Histopathological analysis of diagnostic pre-treatment biopsies and breast tumour specimens will be conducted at Cancer Research UK (Cambridge Biomedical Campus; Addenbrooke's Hospital Site) and/or Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust (CUHNHSFT) . The study will utilise this pathology and genomic information for correlation with MR and PET hypoxia imaging biomarkers.

The diagnostic histopathology slides from the surgical resection, or the pre-treatment core biopsy in patients that have received neoadjuvant therapy will be requested. The H&E stained slides will be assessed manually and then scanned for automated image analysis to correlate histological features, such as lymphocytic infiltrate, presence of necrosis and stromal characteristics, with the imaging findings. A representative diagnostic tumour block will be selected and sections taken for immunohistochemical staining to assess tumour vascularity, markers of tumour hypoxia and

metabolism, and other markers of interest. If there is sufficient diagnostic material available, cores of tissue will be taken for DNA and RNA extraction to allow molecular profiling of the tumour and its microenvironment.

No additional tissue samples will be generated from the participating patient population.

8. Ethics

8.1 Participant Confidentiality

Data and images will be anonymised at source. Each participant will be identified by a unique study number on all study related documentation throughout the course of the trial and data analysis process. The personal data recorded on radiological images will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. Any data transferred will be done according to the NHS Code of Practice on Confidentiality.

8.2 Other Ethical Considerations

There are very few risks attached to having an MRI examination, which is considered a safe non-ionising imaging technique. Some people (less than 5%) find the MR system claustrophobic, however the radiographer conducting the scan will maintain visual contact and talk to the patient between sequences and will stop the scan if necessary. A personal alarm is also given to the patient at the beginning of the examination, the patients can use the alarm to seek assistance and stop the scan at any point during the examination. The MR system is noisy, but ear protection is provided. Patients will be screened prior to commencement of the study for any contraindications including kidney problems or past history of adverse reaction to contrast agents to avoid the occurrence of an allergic reaction.

In the patient study, the BOLD research sequence will be appended to the MR examination conducted as part of standard clinical care, to avoid the need for increased numbers of visits. The research MRI exam will last approximately 20 minutes longer than a standard breast MRI examination. Every effort will be made to minimise the time involved and discomfort of the patient.

Patients participating in studies with carbogen have reported symptoms of breathlessness caused by the carbon dioxide concentration[19]. Further studies have used hyperoxic hypercarbic gas with a lower CO_2 composition, which is much better tolerated by patients[18,24]. A clear explanation of what to expect will be given to all participants. Any discomfort to participants should be minimised by administering carbogen in short blocks, interleaved with either medical air or oxygen.

The PET scan uses the radioactive tracer ^{18}F-FMISO which has been used in human studies for more than 15 years without any serious side effects, but it does emit ionising radiation. The radioactivity disappears from the body within a few hours through the urine. There is also a small radiation dose from the CT imaging aspect of the study. The total radiation dose for both the PET and CT scans is comparable to the natural background radiation that could be expected from living in East Anglia for 2 years[41]. This radiation dose carries a risk of cancer (fatal or non-fatal) of 1 in 4700. This can be considered in the light of the natural incidence of fatal cancer, which is of the order of 1 in 4.

Although it is extremely unlikely that an allergic reaction or other side effect will occur, there are facilities in place within the MRIS Unit, Wolfson Brain Imaging Centre and Addenbrooke's hospital to deal with them. Placing a cannula into a vein can cause some discomfort and very occasionally can lead to infection, but this is highly unlikely in the short time it will be in place. Some people can get bruising at the site where the cannula is inserted. This procedure is performed regularly in the hospital and is generally very safe. The cannula will be inserted just before the scan and will be removed immediately afterwards.

There is a possibility of discovering unexpected abnormalities in the volunteers. This risk will be fully explained on the participant information sheets, along with the plan for managing this. All examinations will be formally reported by a qualified radiologist and nuclear medicine consultant, and any additional clinical information found will be communicated to the oncologist responsible for the patient care or to the General Practitioner of the volunteer.

8.3 Results and publication policy

Study results will be presented at both national and international meetings. Manuscripts will be devised for publication in peer-reviewed scientific journals. Any publication, transmission or presentation of images will comply with the provisions of the Data Protection Act 1998.

9. Data Handling and Record Keeping

All study data will be stored on an internal DICOM server (used for all Radiology research studies). The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file. Data sets generated from this study may be made available without cost to internal researchers involved in basic, translational or clinical breast cancer research, and/or use in other research studies in breast cancer. Any data shared will be fully anonymised and made available for use upon request to the PI of the project. All of the above will be conducted in compliance with the Data Protection Act 1998.

10. Financing and Insurance

The NIHR Biomedical Research Centre is funding this research. The study is covered by NHS and professional indemnity insurance. The study design is covered by University of Cambridge clinical trials insurance.

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School of Clinical Medicine

BRAID

Full Study Title (including acronym):

BRAID Breast Screening – Risk Adaptive Imaging for Density

IRAS Ref: 251317

Date and Version No: 12.05.2022 V2.2

Chief Investigator:

Professor Fiona J. Gilbert
Professor Paul Pharoah, Clinical Epidemiologist

Investigators:

Professor Stephen Duffy, Study Statistician
Professor Antonis Antoniou, Statistical Geneticist
Dr Nisha Sharma, Principal Investigator, Leeds
Dr Sarah Vinnicombe, Principal Investigator, Cheltenham
Dr Sarah Savaridas, Principal Investigator, Dundee
Professor Douglas Easton, Co-Investigator, Geneticist
Dr Yit Lim, Principal Investigator, Manchester
Dr William Teh, Principal Investigator, Royal Free Hospital
Dr Tamara Suari Principal Investigator, St Bartholomew's
Dr Elisabetta Giannotti, Principal Investigator, Nottingham
Dr Archana Seth, Principal Investigator, Glasgow
Dr Reena Aggarwal, Principle Investigator, Leicester

Sponsor:

Cambridge University NHS Foundation Trust and
University of Cambridge
Cambridge Biomedical Campus
Hills Road
Cambridge
CB2 0QQ

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
10	2.2		Fiona Gilbert Johanna Field-Rayner	Second round imaging now to be at 12-18months No second round imaging if recruited within 12 months of end of recruitment period Adding Dundee back in as a site Adding Leicester as a site Clarification of amendment numbering Minor administrative corrections
9	2.1	07/12/2021	Jaimie Taylor	Change Nottingham Site PI from Dr. Jonathan James to Dr. Elisabetta Giannotti. Deleted Dr Dr Sarah Savaridas as PI Dundee and withdrew the site Dundee. Corrected multiple typographical errors throughout.
8	2.0	09/11/2021	Fiona Gilbert Jaimie Taylor	Update the PIS for Scottish site taking into account the following information: The equivalent to the National Cancer Registry data in Scotland is Scottish Cancer Registry and Intelligence Service (SCRIS): https://beta.isdscotland.org/topics/scottish-cancer-registry-and-intelligence-service-scris/ and that Public Health Scotland (PHS) is the data controller for these data. no more patients will be added to part A of the study due to difficulties in recruitment and the reader study associated with this will not be undertaken. Added Nottingham, Glasgow and Dundee as sites and Dr Jonathan James, Dr Archana Seth and Dr Sarah Savaridas as PI's respectively. New post assessment letters submitted. One for no further investigation and one for further investigation. Added a link to the BRAID study website to invitation letters and protocol for more information on breast density. E-Consent is now available and preferable method of recruitment, protocol updated. Changed wording in section 7.3.2 of protocol V2.0 to reflect this. Due to the COVID - 19 pandemic and the subsequent suspension to the study, the

				study timeline for recruitment is to be extended until 31/03/2023. Change wording throughout protocol to allow for scanning outside of 6 months from baseline FFDM for those women approached or consented prior to COVID-19 recruitment halt. Update the protocol to state that invites can be sent either with or after the screening result. Protocol V2.0, section 7.2 & 7.3 have been updated to reflect this. Updated Protocol V2.0 according to the Data Protection Act 2018 with the General Data Protection Regulation (GDPR), as it still mentions the Data Protection Act 1998? In May 2018 these came into force and the previous data protection act repealed. Amend NCRAS to National Cancer Registry held by Public Health Scotland. SAE form no longer in the Appendix. Removed wording in Protocol V2.0 referencing the appendix in section 9.1, also updated the SAE reporting process to be eCRF preferably and if paper to be submitted by email rather than fax. Updated index to reflect the removal of appendix 17.4. Protocol v2.0 Amended for consent to be optional for saliva collection. Changed Protocol v2.0 wording to say that all BIRADS C&D eligible for trial. Revised wording in all invitation letters as there has been feedback from several participants that they were rather alarmed to find out that they had dense breasts and that this inferred an increased risk of breast cancer. Implemented a feedback letter for the control arm to inform them of the ways in which they can mitigate their risk, model the information we provide on the information used in the MyPeBS study. Amended Normal results letter to include breast cancer risk mitigation information as per the feedback letter for the control arm. I also amended the wording slightly, to not include information about the breast unit (not necessary) or the next round of imaging (so this template letter can be used for second round imaging too) and added the date of the appointment so it is clear which round of supplementary imaging this letter refers to. Amended wording around risk associated with density to cause less alarm. Changes duplicated across all invitation letters. In MRI reading instructions changed wording: *without reference to the 2D screening mammogram from the same time-point* to *with reference to the 2D screening mammogram from the same time-point.* Removed the wording: *without*

				reference to the study entry 2D screening mammograms. A new letter to inform our 18-month ladies of their normal scan results by the use of a clinically produced letter.
7	2.0	20/07/2021	Fiona Gilbert Jaimie Taylor	Localising of approved study documents for use in Scotland and addition of Scottish Sites
3	1.2	2/12/2020	Fiona Gilbert Miranda Townsend	Approval of patient facing questionaires
2	1.2	21/11/2019	Fiona Gilbert Miranda Townsend	Minor amendment to add the Royal Free Hospital as a site
1	1.2	14/10/2019	Fiona Gilbert, Miranda Townsend Jenny McGirr Nicholas Payne	Inserted the titles of all investigators and removed investigators no longer working on the study. Added the CanRisk questionnaire and the saliva kits to the pilot study throughout the protocol Removed 14the table in section 6.1 showing the estimation of the recruitment per site for part B Changed wording in sections 7.2 and 7.3 to reflect changed wording in part B recall PIS Added wording to clarify the reading & reporting method for each imaging modality in sections 7.5.2 and 17.2 Updated wording for SAE / SADE definition and removed Safety reporting form from appendix Corrected typos and formatting errors throughout protocol 3. Protocol section 7.5.2.3: Would be better having arbitration by an independent 3rd reader New wording: If possible, arbitration will be by different readers. However, arbitration needs to be pragmatic and timely so can be performed by the same readers if necessary. 4.Protocol section 7.5.2.4: Images will be read independently by two readers without 2D screening mammograms. Therefore, you must have access to the prior mammograms – this is trial of supplementary screening after all. If you don't have the mammograms it may affect specificity

				7.Protocol section 6.1: 7. Protocol section 6.1: Removed individual site target table as this will change as we add new sites- The image targets for the whole study is in the text. 8. Protocol section 9.1: Amend protocol to state that only SAE's related to the trial should be recorded. This is a minimal intervention trial in a screening setting. Death is not a study endpoint. New wording: Only Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADE) related to the trial should be reported. 9. Protocol section 7.4: The protocol states that consent will be done before eligibility check when it should be the other way round. New wording: After confirmation of eligibility and completion of consent, participants will be informed of their randomised arm by the site staff. 14. Patient information sheet states that woman will receive results of supplementary imaging in post- Created letter template for this 15. Created an appointment letter template to send out to women coming back for supplemental imaging 17. (IRAS A28) We would like to send out BRAID Poster with invite as more eye catching. This was originally approved to be used on the wall in the screening clinics. Therefore, I have amended it slightly to make it suitable to be received by individual woman in the post and will call it a Flier for clarity. 18. Protocol section 7.2: We would like to be able to send out a second study invite to women who do not respond to the first invite within 4 weeks. 19. Protocol section 7.5.1.2: New wording: “samples should be stored at the individual sites and collection/transportation will be arranged by the sponsor in batches”. 21. We would like to collect optional saliva samples from patients in Part A as well as part B. The rationale for doing it is that we need to do it for the part B women attending assessment. Therefore, the process needs to be piloted.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
..../...../.....

Name (please print):

.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):

.....

KEY STUDY CONTACTS

Chief Investigator	Professor Fiona J Gilbert University of Cambridge Department of Radiology Level 5, Addenbrooke's Hospital Cambridge Biomedical Campus Hills Road Cambridge CB2 0QQ Tel: 01223 746439 Fax: 01223 330915 fjg28@cam.ac.uk Professor Paul Pharoah University of Cambridge Strangeways Research Laboratory Worts Causeway Cambridge CB1 8RN Tel: 01223 740153 paul.pharoah@medschl.cam.ac.uk
Study Co-ordinator	Jaimie Taylor University of Cambridge Department of Radiology Level 5, Addenbrooke's Hospital Cambridge Biomedical Campus Hills Road Cambridge CB2 0QQ Tel: 01223 336892 Fax: 01223 330915 BRAID@medschl.cam.ac.uk

Sponsor	Cambridge University NHS Foundation Trust and University of Cambridge Cambridge Biomedical Campus Hills Road Cambridge CB2 0QQ
Funder(s)	CRUK GE healthcare Bayer Pharmaceuticals

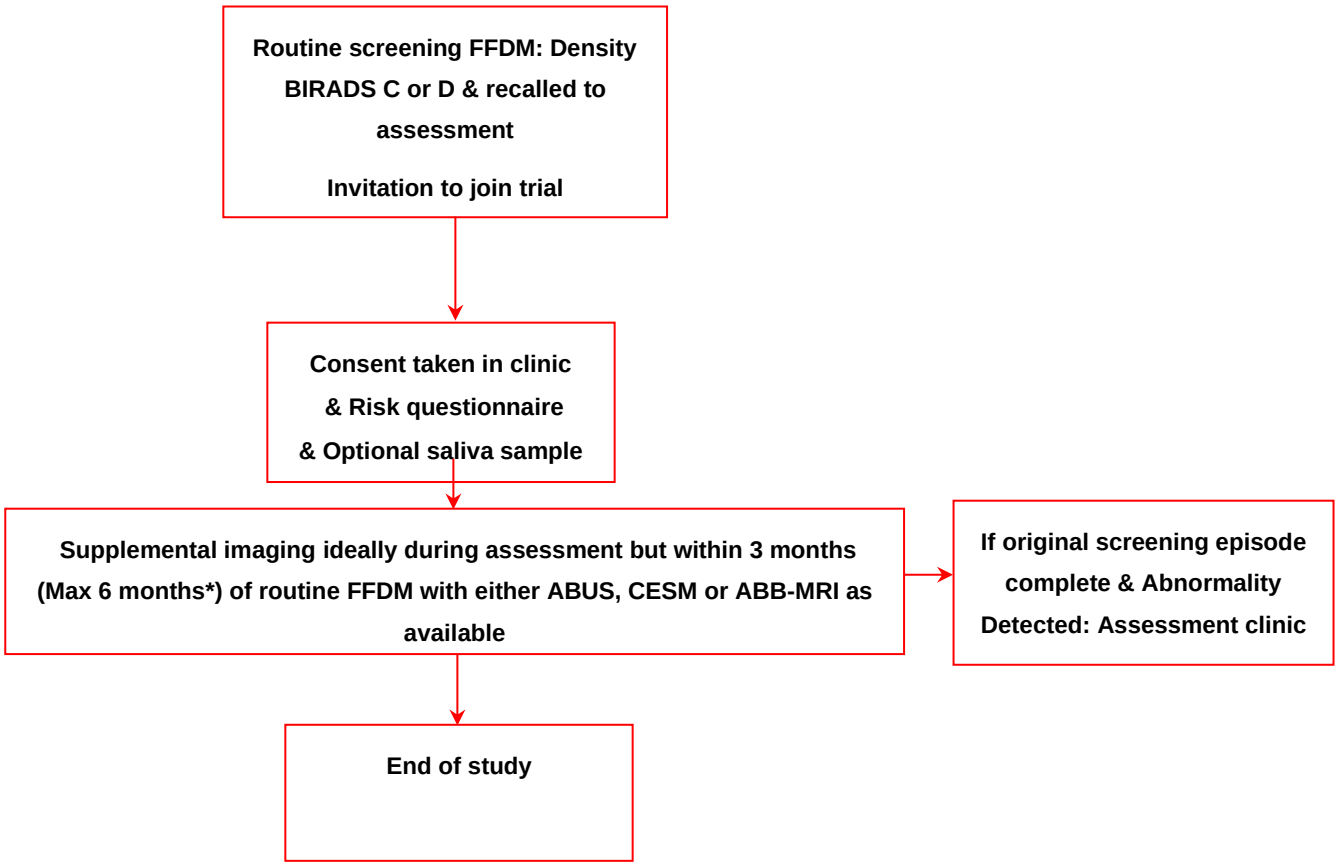
CONTENTS

1 SYNOPSIS

Study Title	**BRAID**: **B**reast Screening – **R**isk **A**daptive **I**maging for **D**ensity
Internal ref. no.	A095053
Study Design	There are two parts to this study: Part A: A non-randomised pilot study of the supplementary imaging techniques being used in part B. No more patients will be added to part A of the study, from 06/2021, due to difficulties in recruitment and the reader study associated with this will not be undertaken. Part B: A Phase 3, multi-centre, randomised cohort study balanced by centre
Study Participants	Women with high breast density (all BIRADS C&D eligible) identified during routine mammographic screening Part A will include women who are being seen in assessment clinics after being recalled from their screening mammogram Part B will include women who are recalled for assessment and those whose screening mammogram is normal.
Planned Sample Size (if applicable)	Part A: 1,200 Part B: 8400
Follow-up duration (if applicable)	Part A: None Part B: 3 years
Planned Study Period	Part A: The pilot study will commence as early as possible in quarter two of 2019. After approximately 10 cases per modality, per site the primary objective of the pilot will be met and part B may begin. No more patients will be added to part A of the study, from 06/2021, due to the difficulties in recruitment and the reader study associated with this will not be undertaken. Part B: Recruitment is planned to commence in June 2019 and to take 18 months. Women recruited within the final 12 month recruitment period of the study, will not be eligible for a second round of imaging. The end of trial will be when the outcome of the subsequent three yearly standard screening mammogram is available for the last participant to be enrolled.
Primary Objective	Part A: For sites to gain experience of imaging assessment cases with the new techniques and to undertake quality assurance to ensure consistency of acquisition and reporting across the sites.

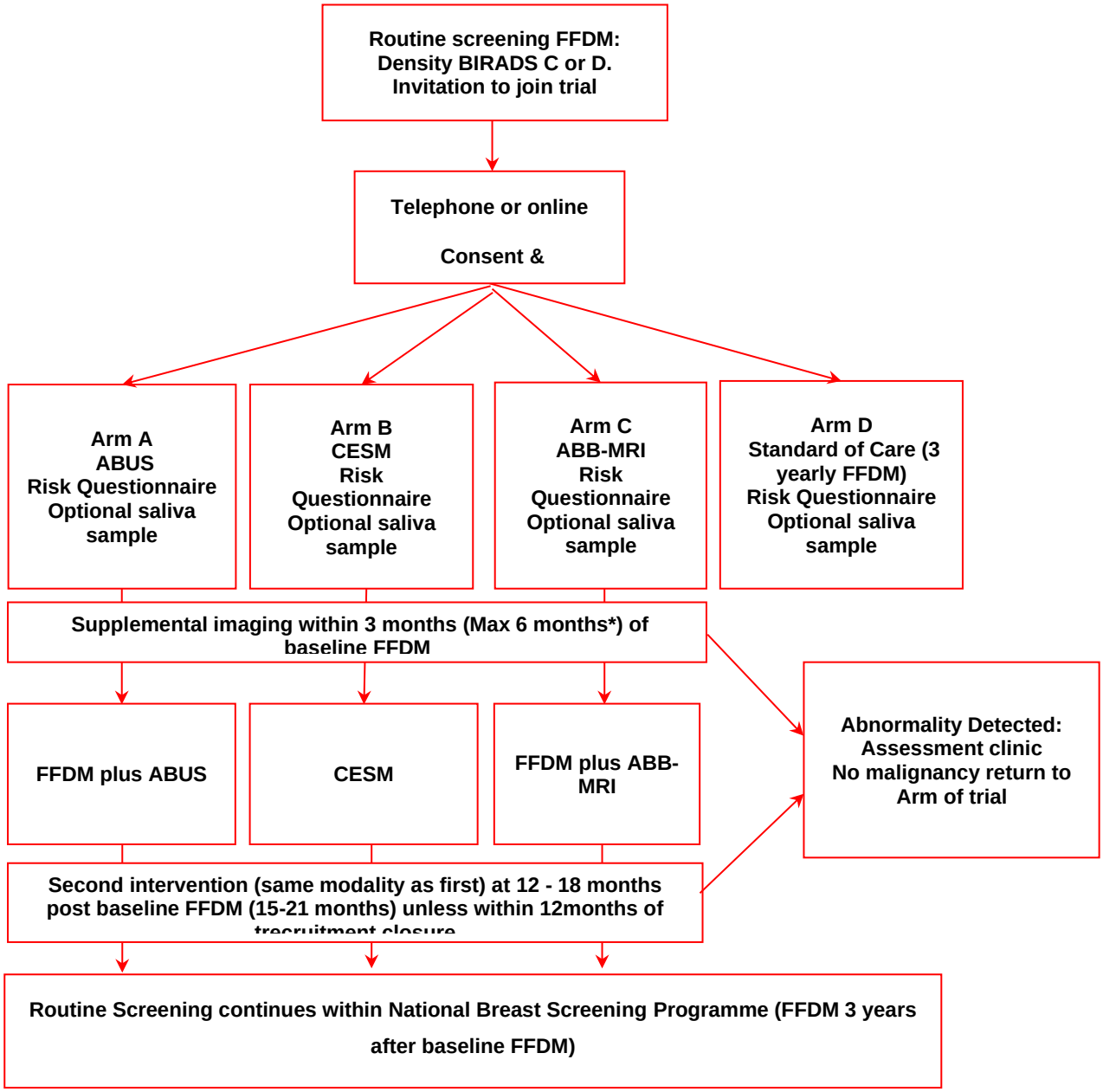
	Part B: To assess the impact of supplemental imaging on the detection of breast cancer in women with dense breasts. The hypothesis is that more cancers will be detected at an earlier stage with the addition of supplemental imaging.
Secondary Objectives	Part A • To assess the feasibility of carrying out additional supplementary imaging in the assessment population • Pilot the recruitment methodology • Pilot the data collection tools • Pilot a participant facing version of the CanRisk questionnaire Pilot the optional saliva sample collection processes • To collect a dataset with sufficient cancers to undertake a retrospective reading study across sites Part B Comparison of a number of clinical indicators from ABB-MRI, CESM and ABUS with standard 2D FFDM. Analysis will include: • Incidence of stage II or worse breast cancers over the period of observation (at first or subsequent screening, symptomatically diagnosed between screening episodes, symptomatically diagnosed following non-attendance for screening). • Detection rate of all breast cancers by stage • Detection rate of all breast cancers by biological type • Detection rate of all breast cancers by size • Interval cancer rate • Stage of interval cancers • Size of interval cancers • Recall rates at prevalent and incident round • Reading time of each examination

2 STUDY FLOW CHART PART A



* However, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible.

3 STUDY FLOW CHART PART B



* However, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible.

4 BACKGROUND AND RATIONALE

Over 2 million women aged 50-70 years are screened for breast cancer each year in the UK through the NHS Breast Screening Programme (NHSBSP) with a coverage of 75% in England. The NHSBSP achieves a cancer detection rate (CDR) of 8.2/1000 with an interval cancer (IC) rate of 2.9/1000 (1). In 2015-16, only 53% of the invasive cancers detected were small cancers – defined as those less than 15 mm in diameter (1). The aim of the screening programme is to reduce mortality by detecting small breast cancers and reduce the number of larger and late stage cancers.

4.1 Parenchymal breast density and breast cancer risk

Breast density, a measure of the amount of fibro-glandular tissue, is one of the strongest known risk factors for breast cancer. Breast density can be measured visually on mammography by assigning a three point (2), or four-point scale (BI-RADS 5th edition) (3), or by marking a visual analogue scale (VAS)(4,5) to give percentage density. Several algorithms for automated analysis of the mammographic raw or processed image data have also been developed including Quantra®, Volpara®, STRATUS and Densitas. Subjective assessment is not very reproducible and values derived from the automated tools vary from each other (6).

Based on the BIRADS system for measuring mammographic breast density, the 10% of women with extremely dense breasts are at a 4-fold increased breast cancer risk compared to women with 'fatty' breasts or 1.6-fold compared to the population average risk (7). Density measured by image analysis algorithms has also been shown to be associated with risk and in a comparison of the Volpara® and Quantra® algorithms, Volpara® performed the best with a 3% increase in risk per 10 cm^3 of dense tissue (8). High breast density is also associated with reduced sensitivity of mammography and an increased probability of developing an interval cancer (9) and cancer detection at a later stage. Mammography sensitivity falls to around 60% in the 9% of the screening population with the highest breast density (10). An overview of studies of interval cancers published from the last decade found that interval cancers have poorer prognostic characteristics and survival outcomes than screen-detected breast cancers and they have similar characteristics and prognosis as breast cancers occurring in non-screened women (11). The majority of interval cancers represent either true interval or occult cancers that were not visible on the index mammographic screen; approximately 20-25% of interval breast cancers are classified as having been visible on the previous screen, many as a subtle abnormality (false-negatives). In a review of interval cancers and subsequent round cancers one third were visible in retrospect on the prior

mammograms (12). An analysis of data from the Canadian screening programme found that increased percent density resulted in a higher frequency of interval cancers within 12 months (13).

4.2 Automated Breast ultrasound (ABUS)

Many studies have demonstrated that ultrasound (US) is a good supplemental screening tool for women with dense breast tissue and it is appealing due to its accessibility, relatively low cost, good patient tolerance, and lack of ionising radiation. Berg et al. demonstrated 4.2/1000 more cancers were detected in women at increased risk and with dense breasts using hand held ultrasound and mammography combined than with mammography alone (14). A follow up report of the ACRIN 6666 trial showed similar results with increased cancer detection in women with dense breasts where mammography was normal and cancers were occult (15). In an Italian study, 38% of all screened women had BIRADS C/D breast density and were offered supplemental ultrasound after a negative mammogram resulting in an additional 4/1000 cancers (16). In the Japan Strategic Anti-cancer Randomized Trial (J-START) of 72,998 women between 40-49 years old screened annually with either mammography alone or with the addition of ultrasound the sensitivity improved (77.0%, 95% CI 70.3-83.7 to 91%, 87.2-95.0; p=0.0004) (17).

However, there are drawbacks to using handheld ultrasound as a screening tool, namely the radiologist time required to perform the examination, significant operator dependence, high recall rates, and relatively low positive predictive value. Automated breast ultrasound (ABUS) is undertaken with a large transducer panel placed on the breast allowing the whole breast to be imaged in four views. Automated scanning produces consistent reproducible images acquired by a radiographer or technician. However, radiologist time taken to review images and the concern regarding false positives and high recall rates remains. ABUS has lesion detectability equal to that of handheld imaging (18) and Kelly et al. demonstrated ABUS increased cancer detection rate from 3.8/1000 with mammography alone to 7.2/1000 using both modalities (19). The multi-institutional observational SomoInsight study of 15,000 women with dense breasts, including some with a personal history of breast cancer, found an additional 1.9/1000 cancers with ABUS (20). These tumours were mainly small invasive node-negative cancers. However, the average recall rate in this study was 15% for full field digital mammography (FFDM) and 28.5% for combined FFDM and ABUS. In a single centre Swedish study, 1,668 women with dense breasts had a significant increase in cancer detection rate to 6.6/1000 with the addition of ABUS from a background rate of 4.2/1000 with FFDM alone (21).

Recall rates are higher when US is used as a supplemental tool to mammography compared with mammography alone. In the ACRIN 6666 trial, recall rates with US alone were 21% in the prevalent round dropping to 11% in rounds 2 and 3 compared to mammography recall rates of 12% and 9% (22). In the J-START study the recall rate increased from 9% to 12% with ultrasound (15). The SomoInsight study recall rate was 15% for FFDM and 29% for combined FFDM and ABUS. The Swedish study recall rate increased from 1.4% to 2.3% with the addition of ABUS. The American task force concluded that supplementing the screening mammogram with an US examination finds additional breast cancers in dense breasts but increases false-positive results (23).

4.3 Contrast-enhanced spectral mammography (CESM)

CESM combines iodinated contrast agent with standard mammography to improve lesion conspicuity, particularly in patients with dense background parenchymal patterns. Abnormal blood flow and increased capillary permeability related to neovascularity associated with a carcinoma is imaged in a similar fashion to contrast-enhanced breast MRI. Retrospective reading studies comparing CESM with FFDM have all shown a significant improvement in the sensitivity and specificity of CESM for detecting breast carcinomas (24–29). The patient populations in all these studies were either symptomatic patients or patients recalled to assessment after an abnormal screening mammogram.

CESM compares favourably with MRI for the local staging of breast cancer. Jochelson et al. found equal sensitivity between MRI and CESM for detecting the index cancer, although MRI was less sensitive for additional tumour foci (30). Lee-Felker et al. found that MRI had slightly higher sensitivity for the index lesion, but equal sensitivity for detecting additional tumour foci (30). Both studies showed a significantly improved positive predictive value (PPV) and specificity for CESM compared to MRI, with fewer false-positive interpretations with CESM (see table).

Study	**Number**	**MRI**		**CESM**	
		Sensitivity (%)	PPV (%)	Sensitivity (%)	PPV (%)
Jochelson (2013)	52	96*	85	96*	97
Lee-Felker (2017)	120 lesions in 52 women	99	60	94	93

* For the index lesion

Physiological/benign background parenchymal enhancement can be seen with CESM in a similar manner to that observed in breast MRI and is significantly associated with menopausal status, radiation therapy, hormonal treatment, and breast density (31). The authors also did not find a clear pattern in variation of parenchymal background enhancement across the menstrual cycle.

Most studies have focused on the role of CESM as a second-line imaging test for the local staging of breast cancer. There is good evidence that the lower energy component of the CESM study is equivalent to FFDM when compared using various image quality criteria (32,33), so if CESM is planned then standard FFDM can be omitted. The radiation dose of CESM is around 1.5 times that of FFDM and is well within UK and European quality assurance guidelines. One study used CESM to replace FFDM as the primary imaging test in the symptomatic setting in order to keep radiation dose lower (34). CESM has been used successfully in the assessment of women recalled following screening mammography (28,29). In the study by Lalji et al. (29), diagnostic accuracy was improved in all readers and CESM was found to be a useful problem-solving tool in recalls from the screening programme. In a pilot study, Jochelson et al. compared screening with contrast-enhanced spectral mammography and MRI screening in women at increased risk of breast cancer. Their patient population included intermediate-risk women who had a personal history of breast cancer or had previously been diagnosed with risk lesions such as atypical ductal hyperplasia, lobular neoplasia and radial scars and those with the highest risk, such as mutation carriers and lymphoma patients with a history of chest irradiation. Three cancers were detected in 307 patients – MRI detected all three and CESM detected two (none were visible on FFDM or the low energy component of the CESM study). The positive predictive value was 15% for CESM (2 out of 13 biopsies) and 14% for MRI (3 out of 21 biopsies). The specificity of CESM and MRI were 94.7% and 94.1% respectively. They concluded that CESM could be a valuable screening tool for women at increased risk of breast cancer (35).

4.4 Abbreviated magnetic resonance imaging (ABB-MRI)

While there is considerable evidence for the sensitivity and specificity of breast screening using MRI, there is only indirect evidence of a survival benefit and it is only cost-effective in high risk women (13). However, ABB-MRI is a promising, cheaper alternative that takes one third of the time to perform compared to standard MRI (10 vs 30 minutes), with comparable or reduced reading times (36). The ABB-MRI acquisition protocol is an unenhanced and a single post contrast image which is subtracted to generate a 3D maximum-intensity projection (MIP) image. Kuhl et al. evaluated ABB-MRI in a cohort of asymptomatic women at increased breast cancer risk with negative mammographic imaging. MIP analysis alone, with an average reading time of just 3 seconds, had a sensitivity of 91% and negative predictive value of 99%.

These both increased to 100% with the addition of the T1 post contrast images with a read time of ~30 seconds. Several studies have compared ABB-MRI with standard MRI examination (37–42). A meta-analysis of these reported a total of 169 cancers were detected by ABB-MRI in 1,557 patients (personal communication). Results of the summary receiver operator characteristic curve for the pooled ABB-MRI showed an area under the curve (AUC) of 0.88 compared with 0.92 for standard MRI (personal communication).

Thus, ABB-MRI has an equivalent level of sensitivity and specificity to standard MRI, at a greatly reduced cost. Combined with the lack of radiation and high sensitivity, this rapid MRI protocol has potential in more widespread screening, and further prospective multicentre trials are required to evaluate its performance in a screening setting (43). There remains some concern, however, that ABB-MRI protocol may not be cost effective for women at intermediate risk of developing breast cancer (41).

4.5 Histopathology and molecular markers of screen detected cancers

The original screening studies compared all invasive and ductal carcinoma in situ cancers and survival in each arm of the study. Widespread debate has resulted from the concern that some screen detected cancers are those cancers that might never have been found in the absence of screening (“over-diagnosis”). There is concern that new technologies will increase the detection of “over-diagnosed” cancers. In an attempt to measure this, this study will compare the pathological and molecular features of cancers in each arm detected by the different modalities and interval cancers. It is hypothesised that those modalities using contrast enhancement (CESM and ABB-MRI) are more likely to find higher grade cancers. It is these cancers that are more likely to metastasise and become “killer” cancers.

4.6 Risk stratification

Many factors have been shown to be associated with future risk of breast cancer including age, family history, age at menarche, age at menopause, parity, breast feeding history, alcohol, family history of breast cancer, mammographic breast density, personal history of benign breast disease, and germline genetic variation. In addition to rare, high-penetrance alleles of genes such as BRCA1, BRCA2, TP53, and PALB2, over 160 common genetic variants associated with small increases in risk have been identified (44). Many breast cancer risk prediction models incorporating a variety of different risk factors have been developed with perhaps the most widely used being the Gail (45), IBIS (also known as Tyrer-Cuzick) (46), the Breast Cancer Surveillance Consortium (BCSC) (47), and BOADICEA models (48). Some of these models have been further developed and refined to include newly identified risk factors, although, to date, no published model has incorporated all known risk factors. The IBIS model, recently modified to incorporate common single nucleotide polymorphisms (SNP) and breast density, is being validated in a large cohort of women attending the NHS Breast Screening Programme (the PROCAS study). BOADICEA is the only model that includes the effects of high and moderate risk mutations in BRCA1, BRCA2, PALB2, CHEK2 and ATM and has been recently extended to include the effects of common breast cancer genetic susceptibility variants, mammographic density and the effects of all the known lifestyle, hormonal and reproductive risk factors for breast cancer. This work is carried out as part of the Cancer Research UK CanRisk programme (PI: Antoniou, http://ccge.medschl.cam.ac.uk/canrisk/; co-I: Pharoah; Collaborator: Gilbert) and BOADICEA has been implemented in a novel interface (CanRisk tool) suitable for implementation across the NHS from primary to tertiary care, including screening. A prototype of the CanRisk tool will undergo evaluation in General Practice and in Clinical Genetics in early 2018, prior to wider release. Preliminary results from a prospective validation study using the FHrisk cohort of women enrolled in enhanced screening programmes in the North of England (10,000 women, 419 incident cancers) has found this extended BOADICEA model to be well calibrated in all deciles of predicted risk and to discriminate between affected and unaffected women (AUC=0.776, 95%CI: 0.752-0.800). Similarly, preliminary results from validating the model in Breakthrough Generations population-based prospective study (~80,000 women, 970 incident cancers), suggests BOADICEA, on the basis of family history information and personal lifestyle/hormonal/reproductive risk factor information, is well calibrated in predicting 5-year risks and discriminates well both in women under 50 (AUC=0.706 95%CI: 0.68-0.731) and in

women over 50 (AUC=0.60, 95%CI: 0.57-0.62). The model with SNP and other genetic information is currently also being evaluated in these cohorts. This proposal will: (1) allow the evaluation of the BOADICEA model in the normal screening population and (2) inform the optimal implementation of the CanRisk tool within the NHS screening programme.

4.7 Rationale for Trial

There are several possible breast imaging modalities that could be used to provide personalised breast cancer screening to women with high density breast parenchymal patterns on mammography. However, the performance of different screening modalities in women with dense breasts is not known.

Therefore, women identified as having BIRADS C or D dense breasts on their screening mammogram will be randomised to either an intervention arm with additional imaging at baseline and repeated 18 months (+/-3 months) later or to the control arm with no additional imaging (standard of care).

The primary outcome measure is the cancer detection rate in each arm. Women will be followed up for a total of two subsequent screening rounds, approximately 6 years from informed consent.

5 OBJECTIVES

5.1 Primary Objective Part A

For sites to gain experience of imaging assessment cases with the new techniques and to undertake quality assurance to ensure consistency of acquisition and reporting across the sites

5.2 Secondary Objectives Part A

- To assess the feasibility of carrying out additional supplementary imaging in the assessment population
- Pilot the recruitment methodology
- Pilot the data collection tools
- Pilot a participant facing version of the CanRisk questionnaire
- Pilot the optional saliva sample collection processes
- To collect a dataset with sufficient cancers to undertake a retrospective reading study across sites

5.3 Primary Objective Part B

To assess the impact of additional imaging on the detection of breast cancer in women with dense breasts. The hypothesis is that more cancers will be detected at an earlier stage with the addition of supplementary imaging. The primary outcome measure is the detection rate of breast cancer at screening, but see secondary outcomes in relation to stage of disease.

5.4 Secondary Objectives Part B

Comparison of a number of clinical indicators from ABB-MRI, CESM and ABUS with standard 2D FFDM. Analysis will include:

- Incidence of stage II or worse breast cancers over the period of observation (at first or subsequent surveillance, symptomatically diagnosed between surveillance episodes, symptomatically diagnosed following non-attendance for surveillance)
- Detection rate of all breast cancers by stage
- Detection rate of all breast cancers by biological type
- Detection rate of all breast cancers by size
- Interval cancer rate
- Stage of interval cancers
- Size of interval cancers
- Recall rates at prevalent and incident round
- Reading time of each examination

6 STUDY DESIGN AND METHODS

Part A was a pilot study of the supplemental imaging techniques, the recruitment methods and the data collection tools. After approximately 10 cases per modality have been collected per site, if the primary objective of the pilot is met, recruitment to the main study may begin. If the site is already experienced in the technique, then the site would not be required to wait to collect 10 cases. However, the participants will still be recruited to the pilot study until the full recruitment targets are fulfilled in order to meet the secondary objectives and create a data set for the retrospective reading study.

Part B, the main study, is a Phase 3, multi-centre, randomised cohort study balanced by centre.

6.1 Number of Centres

We plan to include six breast screening centres within this trial; however, we may increase the number of centres if required in order to reach our target recruitment figure.

Each centre will offer at least two interventions of the trial. In part A, each centre will offer women the supplemental modality of their choice depending on the equipment they have available. Recruitment will continue until 400 women have undergone each supplementary technique. The screening centres will each recruit approximately 2000 women over 18 months to part B resulting in 2,100 women in each arm and 8400 women in total. The overall recruitment target for each modality varies per site due to varying availability of equipment and capacity for research on the clinical imaging equipment. We will continue to recruit participants until the target participant completion is achieved in both the pilot and the main study.

6.2 Number of Subjects

We plan to include 1,200 subjects in the pilot study, approximately 400 in each interventional arm. In part B we intend to recruit 8,400 subjects – approximately 2,100 to receive ABB-MRI, 2,100 to receive CESM, 2,100 to receive ABUS and 2,100 to receive no supplemental imaging.

There will be up to 9 sites who will recruit up until the end of March 2023

6.3 Trial Duration

In Part A participants were to be recruited into the study following an abnormal screening FFDM for which they are being recalled for assessment. However, no more patients are to be added to part A of the study, from 06/2021, due to difficulties in recruitment and the reader study associated with this will not be undertaken. The screening FFDM must also show that they have dense breast parenchyma. Women ideally will have the supplementary imaging as part of the assessment episode but as this may not be possible they can have the additional test up to 6 months after their baseline FFDM. However, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible. Once the additional supplementary test has been completed their participation in the study is complete. Target recruitment is expected to take several months. The pilot study will end once the data analysis is complete.

Subjects will be recruited into part B of the study following confirmation of either a normal screening FFDM or an abnormal FFDM which requires recall to assessment. In either case the screening FFDM must also show that they have dense breast parenchyma. Participants should undergo their initial supplemental imaging ideally within 3 months of the screening

FFDM but up to 6 months will be allowed for scheduling conflicts. Additionally, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible. A second round of supplemental screening, using the same modality that was allocated at randomisation, will be scheduled for 12-18months after their baseline FFDM, unless within 12 months of the end of the study, with the exception of those in the control arm. Those women who are randomised to ABUS or ABB-MRI will also have repeat FFDM at this time.Active participation in the study will end once they have their next screening round (i.e. approximately 36 months after consent). Once subjects complete the study they will return to standard care. Target recruitment is estimated to take approximately 18 months - the active part of the study is anticipated to be 36 months. The study will end once the data analysis is complete.

6.4 Subject Withdrawal Criteria

Information regarding potential contraindications to CESM and / or ABB-MRI will be collected in the usual way prior to the randomised procedures. Anyone unable to complete the procedure for whatever reason and subjects that suffer ill-effects from contrast media or the procedure will be withdrawn from the study but analysed in the intention to treat population according to their ongoing consent.

Subjects can also withdraw of their own volition for any reason and without giving a reason. Subjects who withdraw consent will be asked to specify exactly what they are withdrawing consent for with the following options:

- Withdrawing consent to only future interventions (their previously collected data and samples may still be used in analysis and they are happy to be followed-up)
- Withdrawing consent to any future active participation (no more interventions and no more data will be collected but the data and samples already collected can still be used)

As per GDPR guidelines participants' rights to access, change or move their information are limited and if they withdraw from the study any information that has already been obtained about them will be retained and used in the analysis.

6.5 Primary and Secondary Endpoints/Outcome Measures

6.5.1 Primary and Secondary Outcome Measures Part A

The primary outcome measure for the pilot study is the completion of the supplementary test and the secondary outcome measure is the sensitivity of cancer detection and type of cancers by size, stage and biological type.

The outcome measure of the reading study is the comparative range of sensitivity and specificity of the readers for each of the modalities.

6.5.2 Primary and Secondary Outcome Measures Part B

The primary outcome measure is the cancer detection rate in each arm.

Secondary outcome measures are:

1. The sensitivity and specificity of supplemental imaging with ABB-MRI, CESM and ABUS with standard 2D FFDM.

2. Incidence of stage II or worse cancers over the period of observation

3. The risk of developing breast cancer as assessed by the BOADICEA model.

Analysis will include:

- Detection rate of all breast cancers by stage
- Detection rate of all breast cancers by biological type
- Detection rate of all breast cancers by size
- Interval cancer rate
- Stage of interval cancers
- Size of interval cancers
- Recall rates at prevalent and incident round
- Reading time of each examination
- Automated breast density measurements compared with reader assessment

6.6 Study Participants

Participants in the study will be women aged 50-70 who are participating in the NHS breast screening programme and have BIRADS category C or D breast density. Women with a previous history of breast cancer will not be excluded from participating but data regarding their previous breast cancer diagnosis and treatment will be collected at study entry.

6.6.1 Part A inclusion criteria

To be included in the pilot study the participant must meet all of the outlined criteria:

- Willing and able to give written informed consent
- Willing and able to comply with the scheduled supplementary imaging test
- Female
- Screening mammogram that is being recalled for assessment
- Increased breast density identified on current screening mammogram examination (all BIRADS C or D eligible)
- Aged 50-70 and eligible for 3-yearly NHS breast screening

6.6.2 Part A exclusion criteria

The participant may not enter the study if ANY of the following apply:

- Known BRCA carrier or ≥50% risk of being a carrier
- Unable to give informed consent
- Breast implant(s)
- Pregnant or breast feeding

6.6.3 Part B Inclusion Criteria

To be included in the trial the participant must meet all of the outlined criteria:

- Willing and able to give written informed consent
- Willing and able to comply with the scheduled study visits, tests and other procedures
- Female
- Screening mammogram that is either normal or being recalled for assessment
- Increased breast density identified on current screening mammogram examination (all BIRADS C or D eligible)

- Aged 50-70 and eligible for 3-yearly NHS breast screening

6.6.4 Part B Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Known BRCA carrier or ≥50% risk of being a carrier
- Unable to give informed consent
- Breast implant(s)
- Unable to be followed-up for the study duration
- Current participation in another interventional breast screening trial (including but not limited to MyPeBS)
- Participated in part A of the BRAID study
- Pregnant or breast feeding

7 STUDY PROCEDURES AND INTERVENTIONS

7.1 Randomisation

Only part B of the study will be randomised. Imaging will be allocated by the PIs based on local clinic availability in part A until 400 participants are recruited into each arm.

Randomisation for part B will take place prior to participants being approached and consented. Randomisation will be by whole clinic – this is to ease the planning and delivering of supplementary imaging modalities at the local site level and to facilitate recalled women to take part but yet decline supplementary imaging.

Randomisation lists will be drawn up for each centre separately with the appropriate allocations and allocation ratios for that centre by the study statistician. A list of random allocations for each centre will be provided by the study management team and the centre will work their way through it chronologically, recording the clinic code and date alongside the allocation in advance of the clinic taking place. Any woman who subsequently consents to the trial that was screened in the randomised clinic will then be informed of her allocated arm.

Sites must allocate local staff who will complete the randomisations and plan the supplementary imaging clinics who will not be involved in the clinical care of the participants, in the consenting of participants to trial, or in the scheduling of their screening appointment. We recommend that

a local data manager, administrative assistant, or member of the breast screening office be delegated the task of clinic randomisation. Every attempt should be made to limit knowledge of the allocated arm of a clinic or participant prior to their consent within the site's direct care team. If necessary, to aid clinic planning, site staff involved in the participant recruitment process may be informed of a participant's study arm once the participant has verbally indicated their intent to consent to the study. However, participants should not be informed of their randomised arm until after they sign the informed consent form.

Achieved individual allocation ratios will be reviewed at three months and we will alter the batch randomisation ratios if necessary.

Participants will undergo the supplementary imaging modality that they are randomised to at two time-points, within 0-6 months after their baseline FFDM (However, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible.) and within 15-21 months after their baseline FFDM.

7.2 Recruitment

Participants will be approached for the trial after their screening mammogram has been reported and the result letter sent, or invitations may be sent with the screening result letter. All reporting radiologists at participating sites will be asked to assess breast density (via double reading) on all mammograms they report from eligible clinics during the recruitment period. All mammograms that demonstrate BIRADS category C or D density should have this recorded and a visual assessment score of density should also be documented for those women, either on the CRF provided for the trial (which can be retained as source data) or using a suitable local alternative.

A local method for highlighting those cases which are potentially eligible for the trial should be determined at site.

Documentation of the above eligibility assessments should be retained at sites for the purpose of source data verification.

An invitation letter, along with the BRAID Flier and or participant information sheet (PIS) should be sent to all eligible women with or after their screening mammogram result or recall letter. Those women who then contact the study team for more information or to take part can then be provided with the participant information sheet, via email or post, if not sent with the invite. Women will receive a different PIS depending on whether they are being invited to part A, Part B and have a normal result, or part B and are being recalled. The invitation letter will ask the woman to contact the site research staff for more information about the study if they are interested. For those women being recalled to assessment the PIS and/or consent can be given at the assessment appointment. If women being recalled to assessment neither have the time nor inclination to receive additional imaging, we are asking these women in part B at a minimum to consent for their data to be used in the study. This will allow a valid randomised comparison with usual care. Additionally, women in this group may have the additional imaging as per the randomisation if they so choose at a later date, and this particularly should be offered to women who end up being false-positive recalls. To facilitate this the combined informed consent form (ICF) and PIS document for part B recalls has been split into two elements. Element 1 is to consent for data collection only and element 2 is to consent for the full randomised trial. Women who decide to participate in the full randomised trial must sign both elements, with element 2 signed on the same day or after element 1.

In the instance women do not respond to the study invitation within 4 weeks, the study reminder letter can be sent.

7.3 Informed Consent

Informed consent will be obtained prior to the participant undergoing any activities that are specifically for the purposes of the study.

In most instances the first approach will be via invitation letter from the local breast screening office following or with a screening mammogram result. However, women could also be approached by a member of the site direct care team, such as the PI, sub-investigator, research nurse/practitioner or radiographer who is trained in the study and appropriately delegated this task at the study sites in a clinic, at a screening mammogram, or over the telephone.

To supplement any verbal information, written information will be provided in the form of the current version of the appropriate, approved participant information and consent document. All participant facing material will be approved by the REC and HRA prior to use.

Participants will be offered as much time as they wish (within the eligibility timeframes of the trial) to consider their participation. After consideration of the written and verbal information provided, potential participants will be offered the opportunity to ask questions.

Comprehension of the study, what is involved and the potential risks and benefits, will be confirmed by the site staff prior to signing of the consent form. Once the consent form is signed participants will be provided with a copy, another copy will be kept in the local participant record and the original will be retained in the trial site file.

For women who are offered part B of the trial after being recalled to assessment there is an option to consent just to provide data (element 1) or to take part in the full study (element 2). Women deciding to take part in the full study must sign both elements 1 and 2 of the combined PIS and ICF. Women can initially consent just for element 1 and then at a later date consent to element 2, for instance if they receive a normal result after assessment and decided that they would then like to participate in the full trial. In this instance element 1 may be signed on an earlier date than element 2.

In order to minimise inconvenience for the participants, they may return signed consent immediately upon receipt of the form, later by post or email, or by way of an online consent module.

Postal consent

Women who wish to consent by post will need to initial, sign, and date the informed consent form on the day that the consent discussion has taken place with the appropriate, delegated, site personnel over the telephone. Site staff should document the consent discussion in the local participant record contemporaneously. Once the original consent form is received by the site, the individual who took informed consent should sign the consent form and backdate their signature to reflect the true date of the consent discussion. A copy of the final consent form should be returned to the participant by post, a copy placed in their local participant record, and the original retained in the site file.

7.3.1 Email consent

Women who wish to consent should be sent the partially editable PDF version of the current combined PIS and ICF document from a secure NHS email account. They should be advised

to type their initials in the relevant boxes, type their name in the name box, type their name again in the signature box, and type the date in the date box. They should then return this by email for the person taking consent to do the same. A non-editable PDF copy of the completed consent form should then be returned to the participant for their record, added to the local participant file along with a copy of the email correspondence, and retained in the local investigator site file.

7.3.2 Online consent (Part B only)

Online consent is the preferred method of consent for part B, however postal, email and in-person consent may still be utilised as necessary. Site staff will have access to a participant consent module that is linked to the electronic case report form (eCRF). If they and the participant want to use this module to consent, then the site staff will login and prompt the system to generate an email to the participant. The email will contain an encrypted link that will take the participant to the online consent module. For online consent they will need to type their initials and name in the relevant boxes and then to sign and date they will press “submit”. The person taking consent will also need to login to the eCRF and countersign the consent form, this may take place on a different day to the participant however, site staff should document the consent discussion in the local participant record contemporaneously. The eCRF for that subject will have a record of the date and time of online consent, however identifiable data will not be held in any electronic system. Sites will still need to keep a copy of the electronic signed consent form locally for source data verification.

7.4 Screening and Enrolment

This visit can be either virtual (over the telephone and utilising either email, online, or postal consent) or physical at the site’s and the participant’s discretion. After confirmation of eligibility and completion of consent, participants will be informed of their randomised arm by the site staff. In order to facilitate this, relevant site staff will need to obtain the randomisation result from the local person responsible for randomising clinics. Randomisation will be by whole screening clinic in a 1:1:1:1 fashion between the four arms, stratified by study centre.

Randomisation results are available to the site staff immediately upon consent and confirmation of eligibility and should be communicated to the participant at the earliest convenience.

Those randomised to an intervention arm will have their first additional imaging procedure scheduled within a maximum of 6 months of their eligible (baseline) screening mammogram and ideally within 3 months if possible. However, women who were invited or consented to

participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible.

7.5 Study Assessments/Interventions

7.5.1 Risk Assessments

Research risk assessments will be completed for participants in the study. Participants will be informed in the PIS that they will not receive these results during their active participation in the study. However, they can ask their study investigator to communicate their research risk results to them at the end of their active participation should they wish to receive these. Participants should be informed by the investigator that these scores are not clinically validated and anyone with concerns over their personalised risk should be referred for NHS genetics testing.

7.5.1.1 BOADICEA risk Assessment questionnaire

All women in part B will complete the CanRisk questionnaire either on paper or online for the purpose of the BOADICEA risk assessment. Women in part A May be asked to complete the CanRisk questionnaire so that their risk can be assessed The questionnaire includes family history of breast or ovarian cancer, menarche, menopause, parity, weight, height, alcohol use, oral contraceptive use, menopause hormone therapy use, and previous breast biopsies.

All women will be asked to complete the questionnaire at their earliest convenience on entering the trial.

7.5.1.2 Samples for DNA extraction

Optional saliva samples may be collected from participants on attendance for one of their imaging examinations during the study. Every effort should be made by the site staff to collect these optional saliva samples at the first visit to site following randomisation in order to obtain samples from as many subjects as possible. If women are in the control arm of part B and not returning for supplemental imaging, different methods will be tried to get a the optional saliva sample – (posting out the sample pot and asking them to post it back, Inviting women to the

centre to give saliva, inviting them to give saliva when attending hospital or the GP surgery for another reason).

Women will be instructed to spit 2 ml of saliva in a saliva collection kit provided to sites by the sponsor. Samples should be stored at the individual sites and collection/transportation will be arranged by the sponsor in batches. On arrival at the lab, they will be stabilised and stored for future genetic testing. Detailed collection and shipping instructions will be provided to sites in a separate document.

7.5.2 Imaging Examinations

7.5.2.1 Scheduling of Imaging

In order to accommodate local scheduling challenges, the first supplemental imaging examination for those randomised to an intervention arm or those in the pilot study should take place within 3 calendar months of the eligible FFDM. However, an examination conducted within 6 months will still be considered eligible. Additionally, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible.

In the randomised trial a second imaging investigation, of the same modality they were originally randomised to, will optimally be scheduled for 12-18months after the first FFDM, unless within 12 months of the end of the study

For those subjects randomised to either CESM or ABB-MRI who are still having regular menstrual cycles, all supplemental imaging should be scheduled for days 6-16 (inclusive) of the menstrual cycle, wherever possible.

Participation in the trial will be considered complete for all subjects in part B once they have undergone a second screening mammogram within the NHSBSP (i.e. 36 months after the baseline screening mammogram). If a subject declines a further imaging examination they will be followed up for three years from recruitment.

7.5.2.2 Automated Breast Ultrasound (ABUS)

For the sites which are undertaking ABUS examinations, full training will be provided at each site by GE Healthcare to relevant site staff in the acquisition of images. They can also train a

super-user at each site who will then be able to train additional users at their site if required. The acquisition protocol is provided separately by GE Healthcare.

Quality control tests of the Automated Breast Ultrasound Systems (ABUS): This will be based on the protocol outlined in NHSBSP Publication 70. This protocol is intended for use when testing handheld ultrasound equipment. An initial assessment of the ABUS indicates that, where relevant, many of the tests outlined in that protocol can be suitably adapted such that the same levels of assurance about the stability of equipment performance can be given. The limited number of user configurable scan parameters will aid consistency in carrying out the tests, however there is inherent subjectivity in ultrasound quality control (QC). In order to ensure a consistent approach across all three ABUS sites, the physics service based in Cambridge will carry out the six-monthly testing in accordance with NHSBSP Publication 70 using a purpose-built phantom and will approach the relevant Public Health England groups, offering to produce an addendum to that publication to include ABUS. There will also be a requirement for the users of the equipment to carry out briefer but more frequent (weekly and monthly) tests of the equipment to ensure its continued performance between physics testing visits. Instruction and advice on these tests will be provided by the physics team supporting the study.

Quality assurance of ABUS clinical images will be undertaken by the medical physics team. A sample of clinical examinations from each site will be checked at the beginning of the study.

ABUS Reading: Images will be read on a dedicated workstation or workstations with dedicated software. Readers must have completed training in ABUS. Images will be read independently by two readers with reference to the participant's 2D screening mammogram if required with access to prior mammograms. If an abnormality is detected by either reader this will be scored on a 5-point scale and the images will go for arbitration. At least two readers will then perform a consensus read with the screening mammogram from the same time-point to decide whether to recall the participant for assessment. The consensus read will be assigned a 5-point score. If possible, arbitration will be by different readers. However, arbitration needs to be pragmatic and timely so can be performed by the same readers if necessary.

Reader training in ABUS: GE healthcare will provide training to all readers in the form of their U.S. Food and Drug Administration FDA level 3 approved Mastery programme which includes an online module with real cases and a peer-to-peer webinar.

For the pilot part of the study women from assessment clinics will be imaged using ABUS in order to create a training set of normal and abnormal cases. Each site will collect 100 screening

assessment cases which will be transferred to Cambridge to create a test set of cases. Each reader at each site can review all their own cases with knowledge of outcomes in order to gain experience.

7.5.2.3 Contrast Enhanced Spectral Mammography (CESM)

If the subject is pre-menopausal and having regular cycles, then the supplemental imaging examinations should be scheduled for day 6-16 of the menstrual cycle wherever possible.

A detailed acquisition protocol (see appendix) has been developed to ensure that CESM is undertaken consistently across sites. This acquisition protocol should be followed for all examinations undertaken within the study.

Quality control tests of the Contrast Enhanced Spectral Mammography (CESM): Equipment testing will be based on the protocol presented in Oduko et al. [1]. Initial tests on each system will be carried out by the central (lead) physics team, accompanied by the local physics team. Subsequently, the tests will be carried out every six months by the local physics service, in addition to the routine six-monthly tests on the underlying mammography equipment [2] [3].

The tests of the CESM equipment will be carried out using a phantom manufactured by CIRS and will assess the performance and stability of the equipment. If this is not initially available, the phantom described in [1] could be used as an interim measure, and a cross-comparison with the CIRS phantom made later. There will also be a requirement for the users of the equipment to carry out briefer but more frequent (daily/weekly/monthly) tests of the equipment to check the stability of performance between physics testing visits. Instruction and advice on these tests will be provided by the physics team supporting the study.

CESM Reading: Images will be read on a dedicated workstation or workstations with dedicated software. Readers must have completed training in CESM. Images will be read independently by two readers. The low-energy images should be read and reported first, followed by the high-energy images. Readers may refer to the prior screening mammograms as well as the same time-point as the CESM. If an abnormality is detected by either reader this will be scored on a 5-point scale and the images will go for arbitration. At least two readers will then perform a consensus read with the screening mammogram from the same time-point to decide whether to recall the case for assessment. The consensus read will be assigned a 5-point score. If possible, arbitration will be by different readers. However, arbitration needs to be pragmatic and timely so can be performed by the same readers if necessary.

Reader training in CESM: For the pilot part of the study women from assessment clinics will be imaged using CESM in order to create a training set of normal and abnormal cases. Each

site will collect 100 screening assessment cases which will be transferred to Cambridge to create a test set of cases. Each reader at each site can review all their own cases with knowledge of outcomes in order to gain experience. A further training set from Nottingham will be used to enhance training and testing.

7.5.2.4 ABB-MRI

If the subject is pre-menopausal and having regular cycles then the supplemental imaging examinations should be scheduled for day 6-16 of the menstrual cycle.

An acquisition protocol has been developed to ensure that ABB-MRI is undertaken consistently across sites. This acquisition protocol will be provided to the sites separately and should be followed for all examinations undertaken within the study. Regular QA will be undertaken and review of each sites images to ensure good quality acquisitions.

ABB-MRI Reading: Images will be read on a dedicated workstation or workstations with dedicated software to create MIPs. Images will be read independently by two readers with reference to the 2D screening mammogram from the same time-point, readers may refer to prior mammograms. If an abnormality is detected by either reader this will be scored on a 5-point scale and the images will go for arbitration. At least two readers will then perform a consensus read with the screening mammograms from the same time-point to decide whether to recall the case for assessment. The consensus read will be assigned a 5-point score. If possible, arbitration will be by different readers. However, arbitration needs to be pragmatic and timely so can be performed by the same readers if necessary.

Reader training in ABB-MRI: For the pilot part of the study women from assessment clinics will be imaged using ABB-MRI in order to create a training set of normal and abnormal cases. Each site will collect 100 cases. Previously imaged standard protocol MRI which were normal or with cancers <15 mm can be used to create an ABB-MRI examination and supplement the data set. The data set will be transferred to Cambridge to create a test set of cases. Each reader at each site can review all their own cases with knowledge of outcomes in order to gain experience. A further training set from another site may be used to enhance training and testing.

7.5.2.5 Standard of care

FFDM will be undertaken as standard of care, following NHSBSP guidelines. These images will be double-read according to NHSBSP guidelines. Women who are randomised to the

control arm in part B may be asked to provide the optional saliva sample at their next NHSBSP screening attendance or by post.

7.5.3 Subsequent Interventions (Part B only)

Follow-up of their allocated supplemental imaging should be scheduled 12 – 18months after the baseline FFDM, unless with in 12 months of the end of recruitment, and should follow the acquisition protocols as outlined above. At the time of the repeat supplemental imaging those in the ABUS o& AB_MRI arms will also undergo FFDM for comparison. FFDM will be performed as per standard of care and according to NHSBSP quality standards. Every effort should be made by the site to schedule both these imaging tests for the same day to minimise the inconvenience for the participants.

7.5.4 Management of Abnormalities Detected on Supplementary Imaging

For women who are recruited after being recalled to assessment in both parts A&B the assessment episode should be considered closed once all of the standard tests have been completed. If the supplementary imaging can be completed within the assessment timeframes it can contribute to the outcome of the assessment and the type of supplemental imaging performed and the results of the supplemental imaging should be documented in the comments box. However, if the supplementary test is carried out at a later time the original assessment will need to be closed on NBSS.

If an abnormality is detected by the supplementary imaging post-assessment or at 12 – 18months, then this should be assessed as per standard of care - the woman should be recalled for further work up and biopsy within the assessment service. Any cancer diagnosis resulting from supplementary imaging carried out after screening assessment is complete should be recorded as an interval cancer and the breast screening unit should be made aware. This will be documented on NBSS as being an interval cancer from supplemental imaging and a note should be added to the NBSS assessment record in the comments box.

7.5.5 Follow-Up (part B only)

Women remain on the active part of the study for approximately 3 years, which constitutes one screening round. Data from their subsequent NHSBSP screening mammogram will be collected for trial outcomes. Women who are recruited at age 70 or who turn 70 during their participation in the active study will be followed up for any subsequent breast cancer diagnosis but will not be invited for further mammograms.

7.5.6 Long Term Follow-Up (Part B only)

All women will remain being followed up in the study until two subsequent FFDM examinations have taken place and been reported within the NHS BSP (i.e. approximately six years after they enter the study) at which point their participation in the study will cease. Women who are recruited at age 70 or who turn 70 during their participation in the active study will be followed up for 6 years from study entry for any subsequent breast cancer diagnosis but will not be invited for further mammograms.

8 DEFINITION OF END OF STUDY

The end of study is 36 months after the last participant is recruited into part B. We reserve the right to follow up the women up until 72 months after the last participant is recruited into part B however no interventions will be mandatory after a participant has completed 36 months in the trial.

9 SAFETY REPORTING

Adverse events will not be collected for this trial as we are not assessing the safety of the modalities and all modalities are CE marked. Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADE) related to the trial should be reported however.

Definition of Serious Adverse Events and Serious Adverse Device Effects

A serious adverse event or serious adverse device effect is any untoward medical occurrence that:

1) Led to death,
2) Led to serious deterioration in the health of the subject, that either resulted in
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function, or
    - In-patient hospitalisation or prolongation of existing hospitalisation, or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
3) Led to foetal distress, foetal death or a congenital abnormality or birth defect
4) Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Severe contrast reactions should be reported according to the below instructions, sites may wish to keep a local record of other contrast reactions according to local policy however these do not need to be reported to the trial.

NOTE: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event.

9.1 Reporting Procedures for Serious Adverse Events and Serious Adverse Device Effects

A serious adverse event (SAE) or serious adverse device effect (SADE) occurring to a participant should be reported to the Chief Investigator using the study specific safety reporting form within 15 days of the site staff becoming aware of it occurring.

Preferably Safety reporting forms should be completed and submitted within the eCRF, paper SAE/SADE forms should be emailed to braid@medschl.cam.ac.uk

The Chief Investigator will report all SAEs and SADEs to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: ‘related’ – that is, it resulted from administration of any of the research procedures; and ‘unexpected’ –

that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs and SADEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form (see NRES website)

10 DATA MANAGEMENT AND COLLECTION

10.1 NBSS

For women who are recruited after being recalled to assessment in both parts A and B the assessment episode should be considered closed once all of the standard tests have been completed. If the supplementary imaging can be completed within the assessment timeframes it can contribute to the outcome of the assessment and the type of supplemental imaging performed and the results of the supplemental imaging should be documented in the comments box. However, if the supplementary test is carried out at a later time the original assessment will need to be closed on NBSS.

If an abnormality is detected by the supplementary imaging post-assessment or at 18 months, then this should be assessed as per standard of care - the woman should be recalled for further work up and biopsy within the assessment service. Any cancer diagnosis resulting from supplementary imaging carried out after screening assessment is complete should be recorded as an interval cancer and the breast screening unit should be made aware. This will be documented on NBSS as being an interval cancer from supplemental imaging and a note should be added to the NBSS assessment record in the comments box.

10.2 BS Select

A dedicated clinical trials module is being made available by NHSBSP, this should be used to record all women who enter the study. Trial ID, trial arm, baseline density assessment, and next test due date will all be recorded here. A work instruction will be provided to breast screening offices to enable them to manage these client records. Research nurses and other trial health professionals can be given read only access to BS Select to allow them to assist the breast screening office staff with managing the trial recalls.

10.3 Density measurements

These will be recorded by radiologists assigning the BIRADS scale and VAS score and by an automated density tool. The baseline BIRADS and particularly the VAS score may be recorded in the first instance on paper, a template form is provided for this purpose which sites can optionally use. Breast screening office staff should then transcribe these into the trial module

in BS Select. After data has been transcribed the original paper record can be discarded and the record on BS Select can be considered the source.

10.4 Part A

Paper Case Report Forms (CRFs) will be used for the pilot study. A separate database on the test cases will be created with outcome data. Reader test sets results will be collected for all imaging modalities.

10.5 Part B

We intend to use an electronic case report form (eCRF) to collect the data in the main study however this will be dependent on the pilot of the paper CRFs. Anonymised data on each subject will be collected on a dedicated, fully secure study database hosted by the University of Cambridge. The data collected will include the risk information, breast density, and results of supplemental imaging at each round. Histopathological information on cancers, molecular markers, stage of cancer as well as the result of all core biopsies and any additional information from recalls. Data regarding historical cancer diagnoses and treatment will be collected for subjects enrolled who have had a previous breast cancer.

10.6 Images

Images will be acquired with patient identifiable information and held on the hospital PACS systems. Reading at each unit will done on patient identifiable data. Before images are transferred to Cambridge images will be pseudonymised with the allocated patient trial number.

11 STATISTICS

11.1 The Number of Participants

We have powered the study for the comparison of screening sensitivity. 8,400 women will be recruited in total, giving approximately 200 cancers over two rounds (50 in each arm).

Although each person will spend three years (a programme cycle) in the trial, we anticipate that with recruitment taking place cumulatively over the first 18 months, the total duration of the trial will be five years.

Preliminary results suggest that in this high mammographic density, and therefore higher risk, population, we are likely to observe around a detection rate of around 1.2% with FFDM alone and double this figure, 2.4%, with additional imaging. In terms of statistical power, for comparison of any intervention imaging compared with standard of care, to for 80% power to detect this difference as significant, we would need 1,891 screening episodes per group (5% significance level, two-sided testing). We plan to increase this by 10%, recruiting 2,100 per group, a total of 8,400, to take into account increased variation due to additional components of variance implied by the use of network meta-analysis methodology.

11.2 Analysis of Endpoints

Screening sensitivities will be compared among arms using logistic regression, as will recall rates and incidence rates of cancer by stage and biological type. We will use network meta-analysis methods to take account of the multiple treatments, and different treatment allocations by centre (49).

11.3 Interim Analyses

Because clinics rather than individuals are randomised, and because numbers of eligible and consenting women can vary between clinics, it will be necessary to check that the randomisation ratios of clinics are reflected in the proportions of individuals allocated to each regimen. Therefore, achieved individual allocation ratios will be reviewed at three monthly intervals and we will alter the clinic randomisation ratios if necessary.

Once the full recruitment targets to the pilot study have been met an interim analysis to compare the different modalities in the subset of women who are recalled following an

abnormal mammogram will be undertaken. The interim analysis will report on cancer detection, reader detection and the recall rate of each modality.

A further interim analysis will be undertaken after the first round of supplemental imaging has been completed for all the enrolled participants. We will assess and report on primary and secondary endpoints for part B at this time point as far as is possible.

We do not expect any of the interim analyses to impact the future scope of the trial.

12 ETHICAL AND REGULATORY COMPLIANCE

12.1 Consent

The Informed Consent form will be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements. The investigator will ensure that each study participant, or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with their participation.

The investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The informed consent form used for this trial and any changes made during the course of this trial, will be prospectively approved by the REC. The site investigator will retain the original of each patients signed informed consent form

Should a patient require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

12.2 Ethical Committee Review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

The Chief Investigator will submit annual reports to the REC in accordance with national requirements.

12.3 Protocol Amendments

Protocol amendments will be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC.

The only circumstance in which an amendment may be initiated prior to REC approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In the case, accrual of new patients will be halted until the REC approval has been obtained. In the event of an Urgent Safety Measure being instigated during Phase 2 of the study, the investigator at each participating centre will be notified within 48 hours.

12.4 Declaration of Helsinki and Good Clinical Practice

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

12.5 GCP Training

All study staff will hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with individual Trust policy.

12.6 Case Report Form

For the pilot study paper case report forms (CRFs) will be used. For part B we intend to use an electronic case report form (eCRF) depending on the outcome of the pilot of paper CRFs. All data will be transferred into the CRFs which will be pseudonymised. All study data in the CRF will be extracted from and be consistent with the relevant source documents. The CRFs will be completed by the investigator or designee in a timely manner. The timing, completeness, legibility and accuracy of the CRF pages will remain the responsibility of the site investigator. The CRF will be accessible to the study coordinator, data managers and the investigators as required.

12.7 Source Data

To enable peer review, monitoring, audit and/or inspection investigators must agree to keep records of all participating subjects, sufficient information to link records e.g. NHSBSP records, hospital records and samples and all original signed informed consent forms. Source data will include mammogram, CESM, MRI, ABUS, and histopathology reports as well as the relevant NBSS Records and the trial forms on BS Select

12.8 Electronic Data Storage

All study data will be held in a database administered by University of Cambridge. The participants will be identified by a study specific ID number and/or code - their name and other identifying details will not be included in any study data electronic file however, participant NHS numbers and dates of birth will be collected to cross-reference with NCRAS data for follow-up purposes

12.9 Data Protection and Patient Confidentiality

All investigators and site staff involved in this study must comply with the requirements of the General Data Protection Regulation (GDPR) and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold GDPR's core principles. The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by date of birth and a participant's ID number on the CRF and any electronic database. However, NHS numbers will be collected in the eCRF for the purpose of cross-referencing with NCRAS (National Cancer Registry held by Public Health Scotland) data during the trial follow-up. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the GDPR which requires data to be anonymised as soon as it is practical to do so. Study data will be stored for 10 years.

Participating site staff will maintain a master subject identification list in their local Investigator Site File. This will link identifiable participant data to trial IDs but will not be shared with the sponsor. Prior to transfer of any electronic data including raw images to the coordinating centre sites will first redact any identifiable information and the transfer will be via an encrypted digital file with password protection. Any such data stored locally within sites should be within encrypted digital files, within password protected folders and storage media.

Access to identifiable data will be limited to the minimum number of individuals necessary to carry out the study locally. Identifiable data may be accessed by responsible representatives of the sponsor for data monitoring, quality control, audit, and analysis but this will occur at the site concerned and identifiable data will not leave the site.

The data custodian is University of Cambridge (Professor Fiona Gilbert).

13 INDEMNITY AND FINANCE

The trial will be sponsored jointly by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The study will be funded by a grant from CRUK and part funding and equipment will be provided by GE Healthcare.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants

in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for payment of compensation in the event of harm to the research participants where no legal liability arises.

14 PROTOCOL COMPLIANCE AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations and will not be granted.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Repeated deviations from the protocol will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

15 DISSEMINATION POLICY

Ownership of the data arising from this trial resides with the University of Cambridge. On completion of the study the data will be analysed and tabulated and a final study report prepared. Participating investigators will not have rights to publish any of the study data. Funding from CRUK, GE Healthcare and Bayer Pharmaceuticals will be acknowledged within publications. CRUK, GE Healthcare and Bayer Pharmaceuticals will not have the right to review data prior to publication.

It will not be possible to routinely notify participants of the outcome of the study but it is possible for the participant to specifically request results from their PI. This information could be provided to study participants after the study results are published.

We will comply with relevant CRUK data sharing guidelines.

We reserve the right to make the de-identified data and images publicly available for future research both within and outside of the EU.

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17 APPENDICES

17.1 Schedule of Procedures Part B

[A] Only for those randomised to have supplementary imaging

Procedures	**Visits**				
	Screening / Baseline	**Visit 1[A]** (within 6 months* of screening mammogram)	**Visit 2[A] (12-18months after baseline mammogram)**	**End of study (Completion of subsequent round of NHSBSP screening)**	**Long Term Follow-up (on completion of 2 BSP screening rounds)**
Informed consent	x				
Review of the Inclusion / Exclusion criteria	x				
Review of contraindications to the proposed imaging examinations		x	x		
Mammogram	x		x[C]	x[D]	x[D]
Breast history	x			x	x
Medical history	x				
Optional Saliva sample		x[B]			
CanRisk Questionnaire	x				
Imaging with CESM / ABB-MRI / ABUS (according to randomisation)		x	x		
Cross reference of NHS number with PHE held NCRAS data				x	x

[B] For those in the control arm this can be collected by post or at the end of study

[C] Only for those in the ABUS & ABB-MRI arms

[D] Only for those who are still routinely being recalled for screening by NHSBSP (i.e. those aged <71)

* However, women who were invited or consented to participate in the study prior to any recruitment halt due to the COVID-19 pandemic and only where absolutely necessary, are permitted to undergo study imaging beyond the protocol specified 6 months from screening FFDM. Arrangements should be made for those interested women to consent, and be imaged as soon as is reasonably possible.

17.2 CESM Acquisition Protocol

Guidelines for use of Contrast-Enhanced Spectral Mammography (CESM)

Introduction

CESM involves dual-energy acquisitions following the intravenous administration of iodinated contrast agent. During one mammographic exposure two sets of images are obtained: a low-energy (LE) set, equivalent to standard full-field digital mammography (FFDM) and a recombined set displaying contrast uptake. Standard mammographic positioning is used – a medio-lateral oblique (MLO) and cranio-caudal (CC) projection of each breast.

Iodinated contrast has been used for a wide variety of radiographic procedures for many years, and, providing certain precautions are taken (see contra-indications below), has an excellent safety profile.

Imaging should start at 2 minutes post contrast injection and finish by 7 minutes post injection.

Patient Safety

A safety checklist will be completed by the radiologist for each examination – see below.

Absolute Contra-indications for CESM

- Pregnancy
- Lactation
- Iodine allergy
- Inability to give informed consent
- Inability to tolerate mammography

Relative Contraindications

- Renal Failure
- Diabetes
- Taking Metformin containing medication

Administration of Iodinated Contrast Agents and Renal Function Testing

Following the Royal College of Radiologists endorsement of the 2016 RANZCR Iodinated Contrast Guidelines **https://www.ranzcr.com/search/ranzcr-iodinated-contrast-**

guidelines , renal function testing prior to intravenous administration is only required in the following circumstances

a) Known kidney disease (including kidney transplant)

b) Presence of diabetes

c) Women taking a drug containing metformin.

Even in these situations, if eGFR ≥30 then iodinated contrast agent can still be safely administered.

Referral, Documentation and Prescribing

An imaging request form will be used to request mammographic imaging – following completion of the safety checklist, the decision whether to give contrast and proceed with the CESM study will be the responsibility of the radiologist.

As the women undergoing CESM are outpatients, there will be no drug-card onto which contrast can be prescribed. A CESM code on CRIS (Computerised Radiology Information System) will act as a record of contrast being given. This will usually be 100mls of Iopamidol 300 or equivalent per examination, injected via a pump at 3mls/second. These details should also be entered onto the patient safety checklist.

The radiographer processing the examination should enter the contrast details including batch number onto CRIS at the end of the examination (a sticker from the bottle should be retained and attached to the imaging request form, to facilitate this).

Administering Iodinated Contrast Agent

The task of obtaining intravenous access for administering intravenous contrast media can be performed by a medical practitioner or delegated to a suitably qualified healthcare professional trained and certified in cannulation for contrast media administration.

A medical practitioner must be immediately available to attend to the patient in the event of an emergency or complication of iodinated contrast media administration and must be trained in recognising and treating severe contrast media reactions, including anaphylaxis.

- The department will have access to a Crash team on site and there will be a crash trolley in the unit where the contrast is being administered.

- Facilities for the treatment of acute adverse reactions must be readily available and regularly checked in accordance with Trust policy.
- Patients should not be left alone or unsupervised in the first five minutes post IV administration of contrast.
- In the case of contrast extravasation, departmental contrast extravasation policy must be followed.

Following administrated of contrast agent, the cannula should remain in situ for at least 5 minutes post injection and then can be removed

Image Interpretation

The images will be interpreted by two consultant breast radiologists. Images will be read on a dedicated workstation or workstations with dedicated software. Images will be read independently by two readers without reference to the study entry 2D screening mammograms. The low-energy images should be read and reported first, followed by the high-energy images. Readers may refer to the prior screening mammograms but not the one from the same time-point as the CESM. If an abnormality is detected by either reader this will be scored on a 5-point scale and the images will go for arbitration. At least two readers will then perform a consensus read with the screening mammogram from the same time-point to decide whether to recall the case for assessment. The consensus read will be assigned a 5-point score. If possible, arbitration will be by different readers. However, arbitration needs to be pragmatic and timely so can be performed by the same readers if necessary.

Recalled cases will undergo assessment in accordance with breast screening programme guidelines. Investigations at assessment may include additional mammographic views, including digital breast tomosynthesis, targeted breast ultrasound, and any necessary image guided biopsy. Contrast enhanced X-ray guided biopsy is not available and so in any cases which remain indeterminate or suspicious after conventional imaging assessment may require further investigation with breast MRI and MRI guided breast biopsy if appropriate. As always, biopsy cases will be discussed on an individual basis at a multi-disciplinary team meeting (MDT).

17.3 Example CESM patient safety checklist

Contrast Enhanced Spectral Mammography (CESM) – Patient Safety Checklist

Patient Details (Please affix ID label)

Name:
Date of Birth:
Address:
Hospital/NHS No:

Clinical Team:

Radiologist:

_____

Date of procedure:

_____

IV contrast administration record:

Contrast volume: 100 ml ☐

Flow rate: 3 ml/sec ☐

If other, please specify:

_____

Contrast sticker (attach below):

Pre – procedure checklist

Information sheet received? Yes ☐ No ☐

Do any of the following apply to the patient?

Pregnancy Y ☐ N ☐

Lactation Y ☐ N ☐

Allergy to iodine/contrast/drugs Y ☐ N ☐ Please specify:

_____

Renal problems Y ☐ N ☐ Please specify:

_____

Diabetes Y N

Relevant medication e.g. metformin Y N Please specify:

_____

☐ ☐

If YES, please STOP examination.

If NO, proceed below: ☐ ☐

Verbal consent obtained? Yes ☐ No ☐ Any additional comments:

Anaphylaxis box available? Yes No

Post – procedure checklist

Cannula removed? ☐

By:

_____

— ☐ ☐

Any equipment related issues to highlight?

Yes ☐ No ☐

Anaphylaxis box used?

Yes No

Any additional safety issues to note:

_____

_____

Sodium (^{23}Na) MRI for tumour characterisation and assessment of therapy response in breast cancer

Short Title:	Testing a novel MRI technique for breast cancer
Protocol Name:	NaRNIA
Version:	1.0
Date:	07 January 2019
IRAS ID:	260281
REC Reference No:	19/WM/0196

Chief Investigator:

Prof Fiona J Gilbert
Department of Radiology
School of Clinical Medicine
University of Cambridge
Cambridge, UK

Sponsor:

Cambridge University Hospitals NHS Foundation Trust, UK
and
The University of Cambridge, UK

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

Signature Page

I give my approval for the attached protocol entitled NaRNIA, dated 07/01/2019.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor(s).

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: Date:

Name: Professor Fiona J Gilbert

List of Contents

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Key Study Contacts

Chief Investigator	Prof Fiona J Gilbert Department of Radiology School of Clinical Medicine University of Cambridge Box 218 – Cambridge Biomedical Campus Cambridge, UK ☎ 01223 746448 ✉ fjg28@medschl.cam.ac.uk
Study Co-ordinator	Wendy Phillips MRIS Unit Cambridge University Hospitals NHS Foundation Trust Box 162 – Cambridge Biomedical Campus Cambridge, UK ☎ 01223 256419 ✉ Wendy.Phillips@addenbrookes.nhs.uk
Sponsor	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge Research and Development Department Cambridge University Hospitals NHS Foundation Trust Box 277 - Cambridge Biomedical Campus Cambridge, UK ✉ Research@addenbrookes.nhs.uk
Funder	Cancer Research UK - Cambridge Institute

Protocol Contributors

Dr Iris Allajbeu
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
✉ ia359@cam.ac.uk

Ms Gabrielle Baxter
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
✉ gb561@cam.ac.uk

Dr Julia Carmona-Bozo
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
✉ jcc83@medschl.cam.ac.uk

Dr Martin J Graves
MRIS Unit
Cambridge University Hospitals NHS Foundation Trust
Box 162 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
☎ 01223 256417 ✉ martin.graves@addenbrookes.nhs.uk

Dr Joshua Kaggie
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
☎ 01223 746442 ✉ jk636@cam.ac.uk

Protocol Contributors

Dr Roido Manavaki
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
☎ 01223 746442 ✉ rm617@cam.ac.uk

Dr Mary McLean
Cancer Research UK – Cambridge Institute
University of Cambridge
Li Ka Shing Centre, Robinson Way
Cambridge, CB2 0RE
✉ mary.mclean@cruk.cam.ac.uk

Dr Andrew J Patterson
MRIS Unit
Cambridge University Hospitals NHS Foundation Trust
Box 162 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
☎ 01223 256419 ✉ andrew.patterson@addenbrookes.nhs.uk

Dr Elena Provenzano
Cambridge Breast Unit
Cambridge University Hospitals NHS Foundation Trust
Box 97 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
☎ 01223 256154 ✉ elena.provenzano@addenbrookes.nhs.uk

Dr Frank Riemer
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
☎ 01223 256255 ✉ fr318@cam.ac.uk

Dr Ramona Woitek
Department of Radiology
School of Clinical Medicine
University of Cambridge
Box 218 – Cambridge Biomedical Campus
Cambridge, CB2 0QQ
✉ rw585@cam.ac.uk

Collaborators

Dr William Brackenbury
Department of Biology
University of York
Heslington
York, YO10 5DD
✉ william.brackenbury@york.ac.uk

Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes

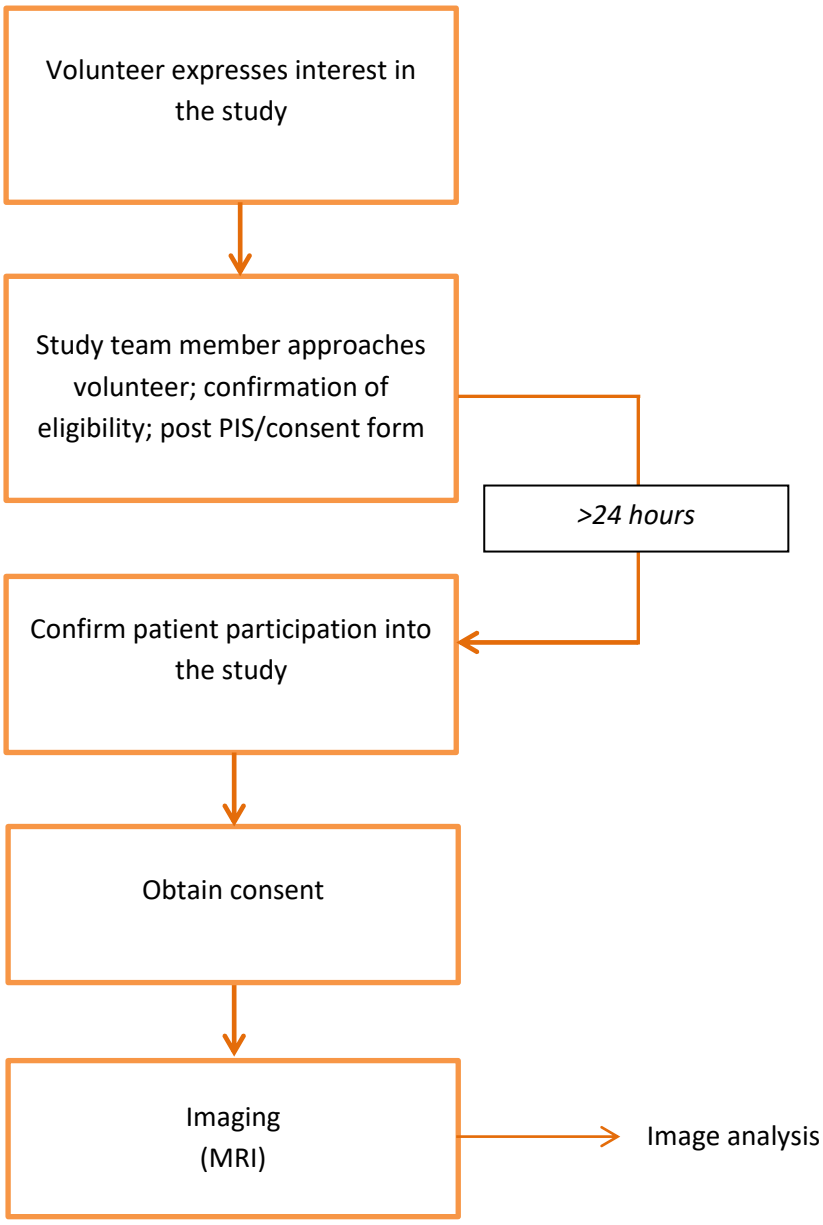
1. Synopsis

Study Title	Sodium (^{23}Na) MRI for tumour characterisation and assessment of therapy response in breast cancer
Study Acronym	NaRNIA
Study Design	Prospective, exploratory, non-randomised
Study Participants	Healthy female volunteers (>18 years). Female patients (>18 years) with pathologically confirmed primary breast cancer
Planned Sample Size	≤20 healthy volunteers and ≤45 breast cancer patients
Planned Study Period	30 months
Follow-up duration	The patient cohort will be followed from their baseline MR or PET/MR examination to their pathological reporting following surgery
Primary Objective(s)	To develop and optimise protocols for the imaging of intra and extracellular ^{23}Na in breast cancer.
Secondary Objective(s)	I. To assess the technical performance of ^{23}Na-MRI for imaging the breast (n≤20 healthy volunteers/n≤30 patients); II. To assess the reproducibility ^{23}Na-MRI of in breast cancer patients undergoing primary surgery (n≤10 patients); III. To investigate the relationship between baseline ^{23}Na-MRI and the grade of breast cancer malignancy (n≤30 patients); IV. To correlate baseline tissue sodium concentration as measured by ^{23}Na-MRI with tissue markers of metabolism obtained from histopathological analysis of diagnostic biopsies/specimens (n≤30 patients); V. To investigate the feasibility of measuring changes ^{23}Na-MRI measurements in breast cancer patients undergoing neo-adjuvant therapy (n≤15 patients).
Exploratory Objective(s)	I. To explore associations between pre and post-therapy correlations between ^{23}Na-MRI measurements and imaging metrics derived from ^{18}F-FDG-PET and multi-parametric ^{1}H-MRI in patients undergoing neo-adjuvant therapy (n≤15 patients); II. To compare and correlate changes between ^{23}Na-MRI measurements and changes in ^{18}F-FDG-PET and multi-parametric ^{1}H-MR imaging indices in patients undergoing neo-adjuvant therapy (n≤15 patients); III. To explore associations between ^{23}Na-MRI and radiological or pathological response in patients undergoing neo-adjuvant therapy (n≤15 patients); IV. To investigate intra-tumoural heterogeneity in ^{23}Na/H-MR and its correlation with tissue markers of metabolism (n≤30 patients).

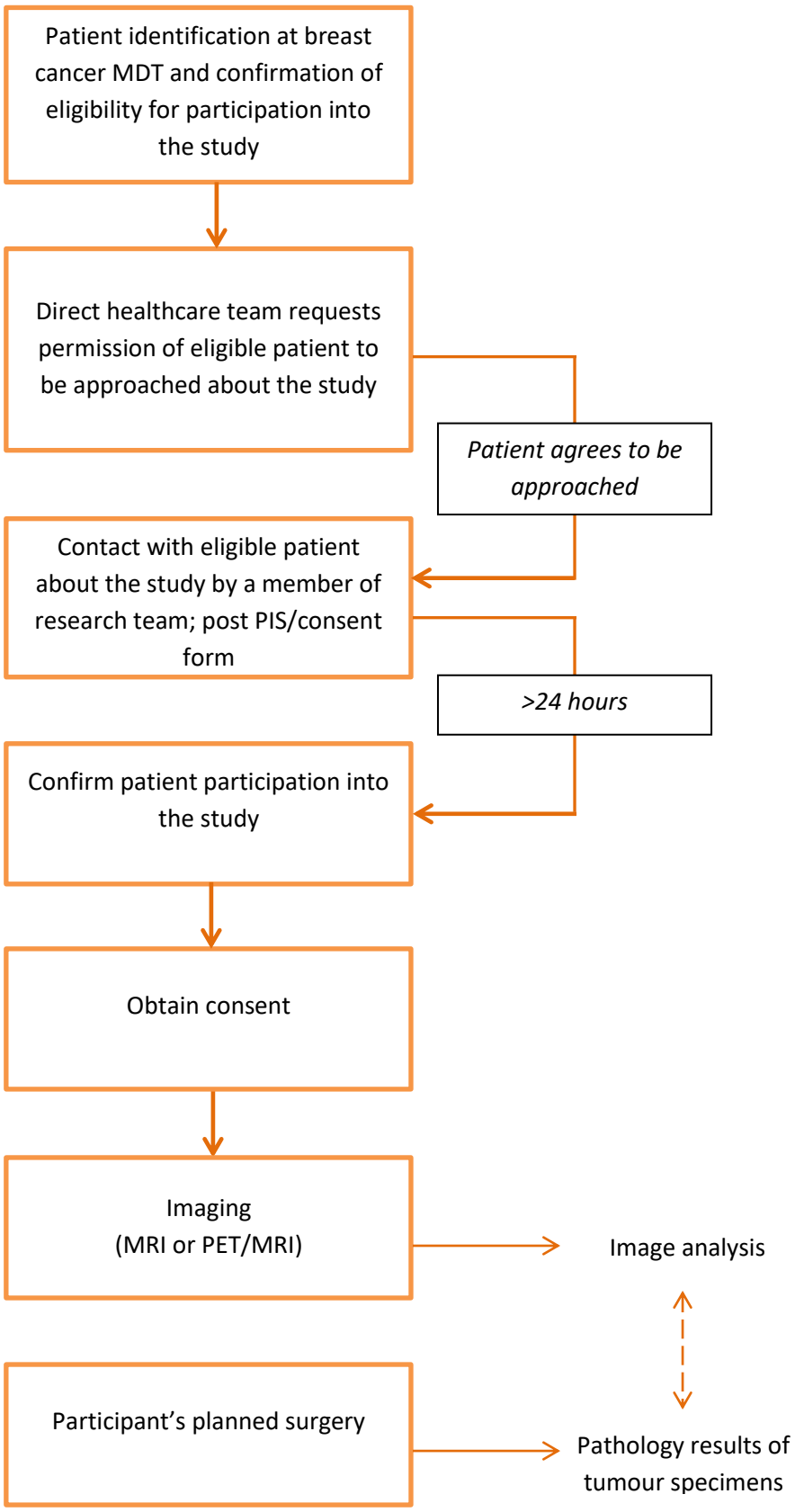
Intervention(s)	This is a prospective, non-randomised, exploratory study on ≤20 healthy female volunteers (>18 years), and ≤45 female patients (>18 years) diagnosed with primary breast cancer. Healthy volunteers (n≤20) will be scheduled to undergo an MR examination at the MRIS Unit, Addenbrooke's Hospital or Wolfson Brain Imaging Centre, University of Cambridge lasting ~60 min. Patients scheduled for primary surgery (n≤30) will undergo an MR examination prior to their planned surgery. The MRI examination will involve ^{23}Na-imaging and last ~75min. MR imaging will be undertaken at the MRIS Unit, Addenbrooke's Hospital or Wolfson Brain Imaging Centre, University of Cambridge, UK. A sub-set of volunteers (n≤10) will be asked to undergo a second MR examination in order to assess repeatability of ^{23}Na-MRI. Immunohistochemical analysis will be performed on surgical tissue specimens to determine tissue markers of interest for correlation with the imaging findings. Patients undergoing neo-adjuvant therapy (n≤15) will undertake up to two (2) combined PET/MR examinations with ^{18}F-FDG subject to obtaining additional consent. PET/MR imaging will be carried out at the Wolfson Brain Imaging Centre (WBIC), University of Cambridge, Cambridge, UK. ^{18}F-FDG will be outsourced by a commercial vendor. Patient imaging will occur at two time points prior to their planned surgery: (*i*) baseline (prior to initiation of treatment) and (*ii*) mid-treatment (after 3-4 cycles of chemotherapy). Patients will receive an intravenous injection of 250 MBq ^{18}F-FDG and undergo a ~75-min PET/MR acquisition, following an uptake period of up to 90 min. MR imaging will be performed simultaneously with PET acquisition. During imaging, up to 4 venous blood samples (≤3 mL) will be collected, in order to determine the radioactivity concentration in whole-blood and plasma. Imaging findings will be correlated with pathological and radiological response. Histopathological analysis will be performed on pre-treatment biopsies for histological markers of interest for correlation with the imaging findings.

2. Study flowchart

2.1. Healthy Volunteers



2.2. Patients


Patient identification at breast cancer MDT and confirmation of eligibility for participation into the study
Direct healthcare team requests permission of eligible patient to be approached about the study
Patient agrees to be approached
Contact with eligible patient about the study by a member of research team; post PIS/consent form
>24 hours
Confirm patient participation into the study
Obtain consent
Imaging (MRI or PET/MRI)
Image analysis
Participant's planned surgery
Pathology results of tumour specimens

3. Background

Breast cancer - the most commonly occurring malignancy in women worldwide - is a highly complex disease, exhibiting a profound degree of heterogeneity and diversity. Despite significant advances in diagnosis and treatment, breast cancer is associated with considerable mortality and treatment-related morbidity [*1*]. The standard clinico-pathological criteria employed in breast cancer diagnosis have shown somewhat limited ability in predicting patient outcome; thus, identification of the best therapeutic regimen for each patient remains unsatisfactory. It is therefore apparent that consideration of a single or a few predictive parameters may fail to capture the complexity of breast cancer. This is particularly important considering compelling evidence that both epigenetics and the tumour microenvironment can highly influence the aetiology, characteristics, progression, and treatment of breast cancer [*2*].

In this context, imaging techniques, like magnetic resonance imaging (MRI) and positron emission tomography (PET), can provide an excellent opportunity for non-invasive and multi-perspective characterisation of breast cancer, as they can interrogate a multitude of cancer-related processes *in vivo*. Although multi-parametric MRI, also including functional information from PET, has been extended to breast cancer [*3*], the exploration of novel imaging approaches that have the potential to improve specificity for the identification of malignancy is still critically needed in breast imaging.

4. Rationale

4.1. Sodium (^{23}Na) MRI in breast cancer

The fundamental abnormality resulting in the development and continued growth of cancers is the continual unregulated proliferation of cancer cells [*4*]. Studies have suggested that the high rate of mitotic activity that characterises abnormal cell growth is initiated by changes in ion transport kinetics and pH levels as a result of sustained depolarisation of the cell membrane and impaired energy metabolism *[5-10*]. Loss of Na^+ homeostasis is a characteristic of neoplasms and a likely direct result of the altered function of various transporters, including the Na^+/K^+ adenosine trisphosphatase (Na^+/K^+ ATP-ase), the Na^+/H^+ exchanger (NHE1), and voltage-gated sodium channels (VGSC) [*11-14*]. In tumours, dysregulation of Na^+/K^+ ATP-ase or impairment of ATP-dependent processes will induce an inwardly directed Na^+ gradient, thereby increasing intracellular Na^+ concentration. Na^+ signalling alterations have been proposed to regulate cancer cell behaviour and play a significant role in remodelling of the extracellular matrix, promoting cancer progression to invasive and metastatic phenotypes [*11*,*15*]. Knowledge about intracellular Na^+ content and its alterations could therefore provide indispensable metabolic information regarding carcinogenesis and tumour malignant progression.

Sodium MRI (^{23}Na-MRI) is a non-invasive tool based on the direct detection of endogenous Na^+ ions in tissues and allows specific assessment of cellular metabolic integrity and Na^+ homeostasis. As physiological and biochemical changes associated with proliferating tumour cells can lead to an increase in tissue sodium concentration (TSC) in tumours compared to surrounding normal tissue, quantitative ^{23}Na-MRI could provide an attractive candidate for the detection and characterisation of tumour malignancy. Studies have indicated an approximately 50-60% increased TSC in tumours relative to that of healthy tissues [*16-18*], most likely due to increases in both extracellular volume fraction and intracellular Na^+ content [*19*,*20*]. However, given that alterations in Na^+ content of tumours are likely to precede changes in vascularity or cellularity as measured with dynamic contrast-enhanced MRI and diffusion-weighted imaging (DWI) respectively, ^{23}Na-MRI could provide direct and more rapid information on tumour metabolism while helping to monitor the effects of therapy [*21*,*22*].

In breast cancer, ^{23}Na-MRI has demonstrated potential for the differentiation of benign and malignant breast tumours and studies have found that an increased TSC in breast tumours could provide for a

sensitive cellular level indicator of malignancy [*23-25*]. Additionally, ^{23}Na-MRI has shown promise as an imaging biomarker for response assessment in patients undergoing neo-adjuvant chemotherapy [*26*].

4.2. ^{23}Na-MRI and multi-parametric PET/MR imaging for the assessment of treatment response to neo-adjuvant therapy.

MRI has an established role in the diagnosis, assessment of treatment response and overall management of breast cancer. The role of dynamic contrast-enhanced (DCE) MRI for the assessment and prediction of breast cancer response to neo-adjuvant chemotherapy has been widely demonstrated [*27-30*]. Although DCE-MRI can provide high-resolution morphological information as well as functional information regarding the vascularity of breast tumours, it cannot provide direct biochemical information about tissue viability. Nevertheless, given the multitude of processes involved in therapy and the multifaceted physiological effects that chemotherapeutic agents can elicit in tumours, mono-modal or sequential multi-modal imaging may not be able to effectively assess treatment response. Studies employing sequential ^{23}Na, proton MR and PET/CT imaging in locally advanced breast cancer [*26*] have previously indicated potential in the use of multi-modal biomarkers to monitor tumour progression and therapy response.

To this end, multi-parametric imaging with a combined PET/MR system, capable of simultaneous PET and MR data acquisition, presents an attractive alternative, as it can afford the ability to collect complementary imaging data, while permitting the macroscopic evaluation of several of processes involved in chemotherapy response. Furthermore, combined PET/MR imaging can allow examination of tumours under the same physiologic conditions, whilst also improving the accuracy with which imaging data are combined. It is anticipated that the methodological and logistical synergies realised by combined PET/MR imaging can facilitate integration of various radiological biomarkers, whilst permitting more effective macroscopic evaluation of several processes involved in treatment response.

4.3. Scope of the NaRNIA study

The scope of this study is the methodological development and optimisation of ^{23}Na-MRI protocols for breast cancer imaging. Methods for ^{23}Na-imaging will be optimised on a cohort of adult healthy female volunteers and applied onto a cohort of breast cancer patients undergoing primary surgery. ^{23}Na-MRI biomarkers resulting from this initial evaluation will be correlated with tumour grade and tissue markers of metabolism.

The study further proposes to utilise biomarkers obtained from ^{23}Na-imaging (cell integrity), ^{18}F-FDG-PET (metabolism), multi-parametric MRI (perfusion, vascularity, cellularity, morphology) to generate parameter maps specific for processes highly related to treatment response in breast cancer. Multi-parametric imaging biomarkers will be correlated with radiological/pathological response indices.

5. Objectives of the NaRNIA study

This pilot research is a prospective, non-randomised, exploratory study in patients with pathologically confirmed breast.

5.1. Primary objective

The primary objective of this investigation is:

I. To develop and optimise protocols for the imaging of intra and extracellular ^{23}Na in breast cancer.

5.2. Secondary objectives

The secondary objectives of this investigation are to:

I. Assess the technical performance of ^{23}Na-MRI for imaging the breast (n≤20 healthy volunteers/n≤30 patients);

II. Assess the reproducibility of ^{23}Na-MRI in breast cancer patients undergoing primary surgery (n≤10 patients);

III. Investigate the relationship between baseline ^{23}Na-MRI and the grade of breast cancer malignancy (n≤30 patients);

IV. Correlate baseline tissue sodium concentration as measured by ^{23}Na-MRI with tissue markers of metabolism obtained from histopathological analysis of diagnostic biopsies/specimens (n≤30 patients);

V. Investigate the feasibility of measuring changes ^{23}Na-MRI measurements in breast cancer patients undergoing neo-adjuvant therapy (n≤15 patients).

5.3. Exploratory objectives

The exploratory objectives of this investigation are to:

I. Explore associations between pre and post-therapy correlations between ^{23}Na-MRI measurements and imaging metrics derived from ^{18}F-FDG-PET and multi-parametric ^{1}H-MRI in patients undergoing neo-adjuvant therapy (n≤15 patients);

II. Compare and correlate changes between ^{23}Na-MRI measurements and changes in ^{18}F-FDG-PET and multi-parametric ^{1}H-MR imaging indices in patients undergoing neo-adjuvant therapy (n≤15 patients);

III. Explore associations between ^{23}Na-MRI and radiological or pathological response in patients undergoing neo-adjuvant therapy (n≤15 patients);

IV. To investigate intra-tumoural heterogeneity in ^{23}Na/H-MR and its correlation with tissue markers of metabolism (n≤30 patients).

6. Study design

6.1. Summary of study design

This is a prospective, non-randomised, exploratory study on ≤20 healthy female volunteers (>18 years), and ≤45 female patients (>18 years) diagnosed with primary breast cancer.

Healthy volunteers (n≤20) will be scheduled for an MR examination at the MRIS Unit, Addenbrooke's Hospital or Wolfson Brain Imaging Centre, University of Cambridge lasting ~60 min.

Patients scheduled for primary surgery (n≤30) will undergo a single MR examination prior to their planned surgery, involving ^{23}Na-imaging and lasting ~75-min. MR imaging will be undertaken at the MRIS Unit, Addenbrooke's Hospital or Wolfson Brain Imaging Centre, University of Cambridge, UK and include a DCE component involving administration of gadolinium-based contrast. A sub-set of patients (n≤10) will be asked to undergo a second ^{23}Na-MR-only examination in order to assess repeatability of ^{23}Na-MRI. Immunohistochemical analysis will be performed on diagnostic biopsies and surgical tissue specimens to determine tissue markers of interest for correlation with the imaging findings.

Patients undergoing neo-adjuvant therapy (n≤15) will undertake up to two (2) combined PET/MR examinations with ^{18}F-FDG subject to obtaining additional consent. PET/MR imaging will be carried out

at the Wolfson Brain Imaging Centre (WBIC), University of Cambridge, Cambridge, UK. ^{18}F-FDG will be outsourced by a commercial vendor. Patient imaging will occur at two time points prior to their planned surgery: (*i*) baseline (prior to initiation of treatment) and (*ii*) mid-treatment (after 3-4 cycles of chemotherapy). Patients will receive an intravenous injection of 250 MBq of ^{18}F-FDG and undergo a ~75-min PET/MR acquisition, following an uptake period of up to 90 min. MR imaging will be performed simultaneously with PET acquisition and include administration of gadolinium-based contrast. During imaging, up to 4 venous blood samples (≤3 mL) will be collected, in order to determine the radioactivity concentration in whole-blood and plasma. Imaging findings will be correlated with pathological and radiological response.

6.2. Study participants

Healthy female volunteers (n≤20), aged 18 years or above.

Female patients (n≤45) aged 18 years or above, with pathologically confirmed primary breast cancer undergoing primary surgery or neo-adjuvant therapy.

The inclusion and exclusion criteria for the study are outlined in Sections 6.2.1 and 6.2.2. below.

6.2.1. Inclusion criteria

- Female, aged 18 years or above;
- Participant is willing and able to give informed consent for participation in the study.

6.2.2. Additional inclusion criteria for patient population

- Pathologically confirmed primary breast cancer;
- Tumour >1 cm diameter on mammography and/or ultrasound.

6.2.3. Exclusion criteria

- Pregnant or lactating;
- History of serious breast trauma within past 3 months;
- Implants known to be contraindicated at 3T MRI;
- Significant or uncontrolled medical problems which according to the opinion of the Chief Investigator render the participant unsuitable for participation in the study;
- Underlying conditions, including but not limited to medical or psychiatric conditions, which in the opinion of the Chief Investigator would preclude the participant from adhering to the study protocol or completing the study per protocol;
- Lacking the capacity to provide informed consent.

6.2.4. Additional exclusion criteria for patient population

- Has undergone chemotherapy or hormonal therapy for breast cancer in the previous 12 months;
- Previous surgery or radiotherapy for breast cancer to the ipsilateral breast within the past 4 months;
- Previous surgery for benign breast disease within the past 4 months;
- History of kidney disease or known allergic reaction to gadolinium contrast agent.

6.3. Study procedures

6.3.1. Participant selection and eligibility

6.3.1.1 Healthy volunteers

Advertisement posters will be placed within Addenbrooke's Hospital and around Cambridge Biomedical Campus, Cambridge, UK to recruit healthy female volunteers into the study. The poster will clearly indicate that participants are going to undergo an MRI scan and provide the contact details (telephone, email) of suitably qualified members of the research team from whom interested participants can obtain more information. Participants fulling the eligibility criteria for healthy volunteers will be invited to participate into the study.

6.3.1.2 Patients

Patients fulfilling the study inclusion criteria will be identified at the breast multi-disciplinary team meeting (MDT). The medical record will be reviewed by the clinician in charge of the patient and/or members of the clinical care team to determine eligibility for the study.

6.3.2. Informed consent

6.3.2.1 Healthy volunteers

Healthy volunteers expressing interest in the study and satisfying the study inclusion criteria, will contacted by a suitably trained member of the research team to discuss the study, describing the overall requirements and any potential benefits and risks arising from participation in the study. Eligible volunteers will be provided with the current REC-approved version of the volunteer information sheet and consent form for review by post or email and given at least 24 hours to consider participation in the study. The eligible volunteer will then be contacted again to discuss any questions they may have regarding their participation into the study. Participation in the study will be allowed, if the Chief Investigator or the member of the research team obtaining consent is satisfied that the eligible volunteer understands the purpose and nature of the MRI examination, and the risks and benefits of participation. Consent will be obtained by an appropriately qualified member of the research team on attendance for the MR examination.

6.3.2.2 Patients

Initial contact with patients eligible for this study will occur at the clinic visit that is part of the initiation of their management scheme. The consultant in charge of the patient or the breast care nurse will introduce the study to eligible patients, explaining that with their permission, an appropriately qualified member of the research team will approach the participant about the study. If the patient agrees to be approached about the study, the Chief Investigator or a suitably trained member of the study research team (e.g. clinical fellow, dedicated research nurse) will contact the patient to discuss the study, describing the overall requirements and any potential benefits and risks arising from participation into the study. Patients will be provided with the current REC-approved version of the patient information sheet (PIS) and consent form for review by post, email or at subsequent hospital visits and given sufficient time (at least 24 hours) to consider participation in the study. The patient will then be contacted again to discuss any questions arising from the study invitation. Participation in the study will be allowed, if the Chief Investigator or the member of the research team obtaining consent is certain that the eligible participant understands the purpose and nature of the investigation, and the risks and benefits of participation. Consent will be obtained by an appropriately qualified member of the research team prior to or on attendance for the MR or PET/MR examination(s).

6.3.3. Imaging

6.3.3.1. MRI scanning

6.3.3.1.1 Schedule

Healthy female volunteers (n<20) will undertake one (1) MR examination involving ^{23}Na imaging lasting ~60 min.

Eligible patients (n≤30) undergoing primary surgery will undertake an MR examination involving ^{23}Na imaging lasting ~75 min on one occasion prior to their planned surgery. A subset of study patients (n≤15) may be invited to participate in a second ^{23}Na-MR examination in order to assess the repeatability of the technique. The ^{23}Na-MR examination performed for the assessment of repeatability will not involve administration of gadolinium-based contrast unless clinically indicated.

All MR imaging will be performed at 3T either or on the GE MR750, MRIS Unit, Addenbrooke's Hospital or the GE Signa PET/MR scanner, University of Cambridge.

6.3.3.1.2 Volunteer and patient preparation

Prior to the MR examination, all study participants will be screened for any contraindications to MRI. Participant height and weight will also be recorded. Participants with contraindications to MR imaging will be excluded from the study.

6.3.3.2.3 Administration of gadolinium-based contrast agent

For participants in the patient arm of the study, a venous cannula will be inserted into one arm for intravenous administration of gadolinium-based contrast agent during MR imaging.

6.3.3.1.4 MR data acquisition

Volunteers and patients will be scanned in the prone position using a dual-tuned ^{23}Na/^{1}H breast coil (Rapid Biomed, Germany). MR acquisition will involve a single bed position covering the entire breast area. For imaging of total and intracellular Na^+ concentration, in-house ^{23}Na UTE sequences will be appended to a standard breast MRI protocol, with the overall scan lasting up to 75 min (~60 min for healthy volunteers).

For participants in the patient arm of the study, the MR examination will also include a DCE protocol, involving administration of gadolinium-based contrast. Patients optionally participating in the ^{23}Na-MRI repeatability scan will not receive an additional injection of gadolinium-based contrast, unless clinically indicated.

6.3.3.2. ^{18}F-FDG-PET/MRI scanning

6.3.3.2.1 Schedule

Eligible patients scheduled to receive neo-adjuvant therapy as part of their treatment plan will undertake up to two (2) MR or combined PET/MR examinations. Stand-alone MR or PET/MR examinations will be performed at:

(i) *baseline* (before the initiation of therapy);
(ii) *mid-treatment* (after 3-4 cycles of neoadjuvant therapy).

Stand-alone MR or combined PET/MR imaging will be performed on the GE Signa PET/MR scanner, University of Cambridge. ^{18}F-FDG will be outsourced by a commercial vendor.

6.3.3.2.2 Patient Preparation

Patients will be required to fast for a minimum 6 hours before each of the combined ^{18}F-FDG-PET/MR examinations. Prior to each PET/MRI examination, patients will be screened for any contraindications to PET/MR imaging. Patients with contraindications to PET/MRI will be excluded from the study. Patient height and weight will also be recorded for subsequent determination of standardised uptake values (SUV).

6.3.3.2.3 Pregnancy screen

Pregnancy is an exclusion criterion for this study, and therefore the possibility of pregnancy in women of reproductive potential will be ascertained prior to participation in the PET/MR imaging procedure on the basis of the standard exclusion rules for PET scans [*31*,*32*]. Eligible participants whose pregnancy status is uncertain will have to undertake a standard pregnancy test on the day of and before participating in the PET/MR imaging procedure. Participants with positive pregnancy test results will be excluded from the study.

6.3.3.2.4 Radiopharmaceutical administration

A venous cannula will be inserted for the intravenous administration of 250 MBq of ^{18}F-FDG. The injected activity will be restricted to ±10% of the target activity of 250 MBq.

6.3.3.2.5 Administration of gadolinium-based contrast agent

A venous cannula will be inserted into one arm for intravenous administration of gadolinium-based contrast agent during imaging. This will be separate from the cannula employed for ^{18}F-FDG administration.

6.3.3.2.6 PET/MR data acquisition

Patients will be scanned in the prone position using a dual-tuned ^{23}Na/^{1}H breast coil (Rapid Biomed, Germany). PET/MR acquisition will involve a single bed position covering the entire breast area. For ^{23}Na-MR imaging, ^{23}Na UTE sequences will be incorporated into standard MRI protocol for the breast. MR imaging will be conducted simultaneously with PET acquisition and include a DCE protocol, involving administration of gadolinium-based contrast.

6.3.3.2.7 Blood sampling and processing

Venous blood samples (<3 mL) will be collected at up four (4) time points post injection in order to determine the radioactivity concentration in whole blood and plasma. Venous blood samples must not be acquired from the injection line. A second venous cannula will be inserted immediately prior to the PET/MR scan. The line from which the blood samples are taken will be cleared by withdrawing a 2-3 mL sample immediately prior to each blood sample to be assayed. The time at which the sample is acquired (relative to the time of injection) will also be recorded. For each participant, the total blood volume acquired during imaging will be ≤30 mL. Analysis of the blood samples will be undertaken at the PET/MR Scanner Suite, Wolfson Brain Imaging Centre, University of Cambridge. Each blood sample will be analysed immediately after it has been obtained. Owing to the time-limited nature of this measurement, the blood samples acquired during imaging will not be stored and will be discarded immediately after analysis.

6.3.3.2.8. Radiation dosimetry

The effective dose (ED) for ^{18}F-FDG has been estimated to be 0.019 mSv/MBq [*33*]. There is no exposure to ionising radiation arising from the MR component of the PET/MR scan. Hence, for an administered activity of 250 MBq, the ED would be 4.75 mSv per PET/MRI examination. The total ED associated with the two ^{18}F-FDG PET/MR examinations that are part of this research protocol is 9.5 mSv. This ED is equivalent to ~4 years of exposure to natural background radiation in the UK [*34*]. Using a risk estimate of detriment of 4.2%/Sv [*35*], the hypothetical risk of cancer (fatal or non-fatal) and

of severe hereditary risks for the total research protocol is 1 in 2506 (~0.05%). This can be considered in light of the natural incidence of fatal cancer, which is of the order of 1 in 3. However, the risk for individuals with a pre-existing medical condition as these participating in this study is small.

6.3.3.4. Clinical assessment of MR and ^{18}F-FDG-PET/MR image data

MR and/or PET images generated by the participating patient cohort will be reviewed by a radiologist experienced in breast MRI and/or a nuclear medicine physician to ensure that no additional sites of disease are present (see Section 10.2; "*Incidental findings*").

6.3.3.5. Analysis of MR and ^{18}F-FDG-PET/MR image data

Alongside participants, sodium phantoms will be placed within the scanner FOV to allow quantification of tissue sodium from the images as previously described [*36*]. The tumour volume (TV) will be defined by an experienced radiologist by drawing regions of interest (ROIs) on several slices of the anatomical or DCE-MRI component of the examination. These ROIs will be superimposed onto the MR and PET image series for subsequent analysis. Sodium in normal appearing tissue will be compared between the patients and healthy volunteers using appropriate univariate statistics. Low-grade and high-grade cancer tissue will be compared between the patient cohort and the healthy volunteers for statistical correlation. DCE-MRI pharmacokinetic modelling will be undertaken and gadolinium concentration over time will be modelled after quantifying baseline longitudinal relaxation (T_1 mapping) and correcting for RF transmit inhomogeneity (B_1^+ mapping).

PET emission data will be reconstructed using iterative reconstruction algorithms, as implemented on the scanner, with corrections applied for attenuation, scatter, random events, dead time, normalisation, sensitivity and isotope decay. ^{18}F-FDG PET registered frames will be utilised for the generation of static parameter maps for the determination of ^{18}F-FDG uptake as standardised uptake values (SUV_{max}, SUV_{mean}, and SUV_{peak}) and tissue-to-plasma ratios (T/P) respectively. For the calculation of T/P, the mean plasma radioactivity concentration of the venous samples acquired during imaging will be utilised as reference.

The relationship between PET, ^{23}Na and multi-parametric MR (e.g. DCE) imaging metrics will be investigated by performing formal statistical analyses to assess the normality assumptions of each respective distribution. Appropriate univariate statistics will then be performed to express the relationship between the various imaging and tissue markers of interest. Relationships between PET and MR biomarkers will be assessed both regionally and voxel-wise. Correlations with pathological and radiological response will also be obtained for data sets obtained from patients undergoing neo-adjuvant therapy.

6.3.4. Histological assessment

Histopathological analysis of diagnostic biopsies and breast tumour specimens will be conducted at University of York, York and/or Cancer Research UK, Cambridge Biomedical Campus, Cambridge. The study will utilise this pathology and genomic information for correlation with MR and PET imaging biomarkers.

The diagnostic histopathology slides from the surgical resection, or the pre-treatment core biopsy in patients that have received neoadjuvant therapy will be requested. The H&E stained slides will be assessed manually and then scanned for automated image analysis to correlate histological features of interest (e.g. presence of necrosis, stromal characteristics) with the imaging findings.

A representative diagnostic tumour block will be selected, and sections taken for immunohistochemical staining to assess tumour vascularity, metabolism, and other markers of interest. If there is sufficient diagnostic material available, cores of tissue may be taken for DNA and RNA extraction to allow molecular profiling of the tumour and its microenvironment.

No additional tissue samples will be generated from the participating patient population.

6.3.5. Timescale

The expected duration of the study is 30 months. Image analysis will be undertaken throughout the duration of the study.

6.3.6. Definition of End of Study

The End of Study is six (6) months after the last participant receives their scheduled breast cancer surgery. This is to allow sufficient time for the study endpoints to be investigated.

7. Safety reporting

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered medically significant by the Chief Investigator

Medical judgement will be exercised in deciding whether an adverse event (AE) is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, will be treated as serious. Hospitalisations for elective treatment of a pre-existing condition will not be regarded as SAEs.

A SAE occurring to a patient will be reported to NRES Committee West Midlands – The Black Country where in the opinion of the Chief Investigator the event was either related to the administration of any of the research procedures outlined in Section 6.3, or unexpected (event not listed in this protocol as an expected occurrence). Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form.

8. Data management

8.1. Data collection

Data and images collected over the course of the study will be stored and analysed by the investigators (see *Section 5.2*; *"Data transfer and archiving"*). For each patient study, the MR and PET/MR acquisition information (patient trial ID, age, weight, height, date and type of scans, injected activity for PET/MR scans, any comments/notes pertaining to the MR or PET/MR data acquisition) will be recorded on the MR or PET/MR acquisition form. As the study will also require the acquisition and assay of venous blood samples during PET/MR scanning, the time at which each blood sample is taken will also be recorded. Study participants will be identified by a study-specific ID on the MR or PET/MR acquisition form and any subsequent study-specific form. Personal data of clinical significance collected during the course of the study will be available to the participant's clinical care team using standard NHS procedures with the consent of the participant. In case of detection of unsuspected clinical abnormality, the General Practitioner of the participant will also be informed, given the participant's consent (see Section 10.2; *"Incidental findings"*).

8.2. Data transfer and archiving

PET and MR images and raw imaging data will be collected and stored using Data Governance policies of the MRIS Unit, Addenbrooke's Hospital and Wolfson Brain Imaging Centre, University of Cambridge. All images will be stored in non-anonymised format in a secure computer environment with data encryption in the MRIS Unit, Addenbrooke's Hospital or Wolfson Brain Imaging Centre, University of Cambridge and may be transferred to Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's Hospital PACS system) for clinical purposes. Raw imaging data in non-anonymised format will also be securely archived on a secure computer server/media with data encryption. Access to non-anonymised images and raw imaging data will be restricted to study personnel and/or staff of the MRIS, Unit and/or Wolfson Brain Imaging Centre, University of Cambridge. Non-anonymised images and raw imaging data will be kept for a minimum of 10 years after acquisition.

Access to images or data for analysis will be in pseudo-anonymised form with all direct identifiers removed and restricted to authorised members of the research team performing the analysis. Data transfers will be performed according to the NHS Code of Practice on Confidentiality.

8.3. Data sharing

The imaging dataset for this project will consist of ≤20 female healthy volunteers and ≤45 female breast cancer patients, undergoing imaging examinations with stand-alone MR or PET/MR. Fully anonymised data sets from this study may be made available without cost to internal researchers involved in basic, translational or clinical cancer research upon request to the Chief Investigator of the project. After participant consent has been obtained and upon permission from the study Chief Investigator, anonymised data sets generated by this study may also be used in other or future research studies. The study may also utilise fully de-identified images/data from other imaging studies in breast cancer, if relevant to this research investigation and where appropriate participant consent for data sharing has been obtained. Inclusion of additional datasets into this research study shall be performed with the permission of the custodian of these data sets and the Chief Investigator of this study. All data transfers will be performed according to the NHS Code of Practice on Confidentiality.

9. Statistics

The study will recruit ≤20 healthy female volunteers, and ≤45 patients with clinically confirmed primary breast cancer, with the aim of optimising ^{23}Na-MRI protocols and assessing the feasibility of ^{23}Na-MRI for breast cancer characterisation.

Due to the exploratory nature of this investigation and the fact that insufficient prior knowledge is not available to permit formal statistical calculations, no statistical techniques were used to determine sample size and sample size sensitivity. To allow evaluation of the primary and secondary objectives of the study, sample size determination has been primarily based on feasibility and pragmatic considerations of the anticipated recruitment rates.

10. Ethics

10.1. Participant confidentiality

Data and images will be anonymised at source. Each participant will be ascribed a unique study specific ID number for use throughout the course of the study on any study-related documentation, and/or any

electronic database. Any personal data recorded on radiological images will be regarded as strictly confidential. Participants' personal information and/or clinical information (where relevant to this study) will be kept securely in the Wolfson Brain Imaging Centre and/or Department of Radiology, University of Cambridge in secure computer systems with data encryption and/or lockable cabinets with restricted access. Access to patient personal identifiable data and/or clinical information (only where relevant to this study) will be strictly limited to members of the research team. Storage and handling of images and data from this study will be performed in accordance with current data protection legislation. If data are shared with collaborators, these will be passed either fully anonymised or by reference to the minimum identifier in encrypted form. All data in the case report form will be extracted from and be consistent with the relevant source documents. Any data transferred will be done according to the NHS Code of Practice on Confidentiality.

10.2. Incidental findings

There is a possibility of discovering unexpected abnormalities in study participants. This risk will be fully explained to the eligible participant on the participant information sheet and during the recruitment process. MR examinations will be formally reported by a radiologist with experience in breast imaging. PET examinations will be additionally reported by an experienced nuclear medicine physician.

Additional clinical information found in patient examinations will be communicated to the clinician responsible for patient care, and the breast cancer MDT. Any co-morbidity and the wishes of the patient will be included in the MDT discussion before proceeding further. The General Practitioner of the patient will also be informed, given the participant's permission.

If an unexpected abnormality of clinical significance is found in healthy volunteers, the Chief Investigator or their designated delegate will discuss the findings with the participant, and with their permission communicate these findings to their General Practitioner.

10.3. Incentives and payment

Participants will be offered reimbursement of travel and parking costs. Travel expenses up to the value of £20 for any visits additional to normal care will be reimbursed on production of tickets or receipts, or a mileage allowance (45p/mile) as appropriate.

10.4. Other ethical considerations

There are very few risks attached to having an MRI examination. Some people (less than 5%) find the MR system claustrophobic, however the radiographer conducting the scan will maintain visual contact and talk to the patient during the imaging examination and stop the scan if necessary. A personal alarm will also be given to patients at the beginning of the examination; patients can use the alarm to seek assistance and stop the scan at any point during the examination. The MR system is noisy, but ear protection is provided. Participants will be screened prior to commencement of the examination for any contraindications to MRI, including kidney problems and history of adverse reaction to contrast agents to avoid the occurrence of an allergic reaction.

Utilisation of the radioactive tracer ^{18}F-FDG as a PET tracer for oncological applications has been documented in standard clinical practice and research studies for almost 40 years, and it is not associated with any toxic effect or serious adverse effects in humans. The ^{18}F-FDG PET scan however does involve exposure to ionising radiation. The total ED for the PET component of the examination is 9.5 mSv (Section 6.3.3.2.8; "*Radiation Dosimetry*"). This ED is equivalent to ~4 years of exposure to background radiation in the UK. The hypothetical risk of cancer (fatal or non-fatal) and of severe hereditary risks for the total research protocol dose is ~0.05%. This can be considered in light of the natural incidence of fatal cancer, which is of the order of 1 in 3. However, for individuals with a pre-existing medical condition as these participating in this study, the risk is considered to be small.

As with any medical procedure, there may be unanticipated side effects. Although it is unlikely that an allergic reaction or other side effect will occur, there are facilities in place within the MRIS Unit, Addenbrooke's Hospital or Wolfson Brain Imaging Centre, University of Cambridge (adjacent to Addenbrooke's Hospital) to deal with them. Placement of a cannula into a vein can cause some discomfort, bruising at the site where the cannula is inserted, and may lead to infection; however, this is highly unlikely in the short time the cannula will be in place. All cannulae will be inserted just before the scan and removed immediately afterwards.

11. Publication policy

The study results will be published in peer-reviewed scientific journals on behalf of the PI and the study collaborators. Any publication, transmission or presentation of images will be in fully anonymised form and adhere with the provisions of the Data Protection Act 2018. No investigator may present or attempt to publish data relating to the study without prior permission from the PI of the project.

12. Financing and insurance

Cancer Research UK (CRUK) will be funding this project (Pioneer Award; award no: C57745/A25922).

The NHS Indemnity Scheme will cover the NHS participants. The University of Cambridge Insurance for Negligence and Non-negligence harm under the University's Clinical Trial Policy is also arranged for this study.

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PROTOCOL

1. Title of Research Project: IMAGING VASCULARITY IN PRIMARY BREAST CANCER WITH NOVEL MRI TECHNIQUES.	
2. Name of Applicant *Surname:*GILBERT *Forename:*FIONA	Title and Position: PROFESSOR OF RADIOLOGY, HEAD OF DEPARTMENT
3. Co-Investigator(s) *Surname:*BRUKER *Forename:*VEREENA *Surname:* JIMENEZ-LINAN *Forename:*MERCEDES *Surname:*EARL *Forename:*HELENA *Surname:*CALDOS *Forename:*CARLOS *Surname:*WALLIS *Forename:*MATTHEW *Surname:*PARTO *Forename:*FOROUHI *Surname:*BENSON *Forename:*JOHN *Surname:*CLAYTON *Forename:*GILL *Surname:*ABRAHAM *Forename:*JEAN *Surname:*HUGHES-DAVIES *Forename:*LUKE *Surname:* GRAVES	Title and Position: Consultant Pathologist Consultant Pathologist Reader in Clinical Cancer Medicine Professor of Cancer Medicine Consultant Breast Radiologist Consultant Breast Surgeon Consultant Breast Surgeon Consultant Breast Surgeon Consultant Medical Oncologist Consultant Medical Oncologist

*Forename:*MARTIN *Surname:*MCLEAN *Forename:*MARY *Surname:*PATTERSON *Forename:*ANDREW *Surname:*BAIRD *Forename:*RICHARD *Surname:*HEARD *Forename:*SARAH *Surname*: BEDAIR *Forename*: REEM	Consultant Clinical Scientist Staff Scientist Clinical Scientist Lecturer in Experimental Cancer Medicine Medical Physicist PhD student
4. Current address: Level 5 Radiology, Box 218 Addenbrooke's Hospital Cambridge Postcode: CB2 0QQ Tel: 01223 746439 e-mail: fjg28@cam.ac.uk email : rb648@cam.ac.uk	Address where research will be conducted: Addenbrooke's Hospital.
5. Lay title of research: ***IMAGING VASCULARITY IN PRIMARY BREAST CANCER WITH NOVEL MRI TECHNIQUES***	

Introduction:

Breast Cancer and the Role of Imaging:

Breast cancer is the second most prevalent disease in women and the leading cause of death in ages 40-59[2]. A primary objective for breast cancer imaging is the early detection and differentiation of malignant lesions. However, an overlap between malignant and benign lesions exists in conventional mammography, resulting in moderate to poor specificity. Alternative non-invasive methods for assessment are well established such as dynamic contrast-enhanced MRI (DCE-MRI). Additional less established MRI techniques include Diffusion Weighted Imaging, ^{1}H Spectroscopy and Blood Oxygen Level-Dependent (BOLD) contrast.

Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI)

DCE is currently used as the de facto standard in breast MRI examination as it has been shown to have a better specificity and sensitivity than conventional mammography [3]. It improves the diagnostic confidence and staging of lesions, as well as providing a surrogate biomarker for monitoring the response to conventional chemotherapy and/or additional pharmacotherapy [4]. DCE involves the intravenous administration of gadolinium (Gd) chelate contrast agent. The differential uptake and washout of gadolinium in tissues results in an increased signal on T1-weighted images. [1, 3, 5].

The introduction of faster sequences has enabled the investigation of contrast uptake with better temporal resolution, allowing pharmacokinetic modelling. DCE-MRI exploits differences in temporal enhancement characteristics between malignant and normal or benign tissues, where most cancers tend to demonstrate rapid, intense enhancement followed by a relatively rapid washout compared to normal parenchymal tissue [1, 6] (figure 1).

DCE-MRI is a relatively non-invasive technique for quantifying tumour tissue perfusion. We plan to investigate the relation of these metrics to histopathology markers of cellular density e.g.: Vascular Endothelial Growth Factor (VEGF), CD-34, CD-31 and proliferation markers e.g.: Ki-67.

Pharmacokinetic (PK) modelling:

While most neoplastic tissues frequently have contrast enhancement patterns that differ from normal breast tissue, it is often difficult for radiologists to differentiate between benign and malignant lesions simply by visually inspecting the contrast-enhanced lesion on the post-contrast MRI. [2, 4]

Semi-quantitative and quantitative models have been proposed to measure the manner in which a lesion takes-up Gd contrast.

Semi-quantitative techniques describe the shape of the Signal Intensity (SI) vs. time curve, the enhancement onset time, maximum SI, gradient of contrast uptake and washout and initial area under the gadolinium curve (IAUGC). [1, 6]

Alternative quantitative techniques depend on characterising Gd uptake curves over time. With PK modelling focused on the kinetic enhancement data, numerical models calculate permeability rate constants and quantitatively determine changes in tissue contrast agent concentration. [1, 4]

For functional analysis of tissue perfusion, Tofts et al proposed quantifying the tracer kinetic parameters using K^{trans} (Transfer constant); representing the trans-endothelial transport of contrast medium from the vascular compartment to the tumour interstitium which provides a measure of vascular permeability[7]. V_e describes the fraction of the tumour volume occupied by the extravascular extracellular space (EES). Evidence from several studies strongly suggests that K^{trans} can be used as a predictive biomarker to determine the response to anti-angiogenic drugs [3, 6, 7]. K^{trans} is generally high in tumours showing a significant reduction in locally advanced breast cancer responding early to neoadjuvant chemotherapy [2, 5]. In addition, an increase in v_e has been shown in non-responders [2, 3]. The choice of arterial input function measurement also impacts on the overall results of tumour vascular heterogeneity[4].

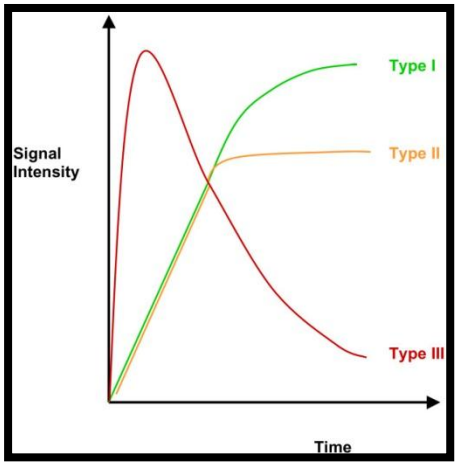

Figure 1: ***Time-signal intensity curve for breast lesions.*** *A type I curve shows progressive enhancement (likely benign). A type II curve plateaus off after an initial increase in enhancement (likely malignant). A type III curve demonstrates immediate washout after a rapid increase in enhancement (high probability of malignancy). [1]*

The availability of 3T MRI scanners allow higher signal-to-noise ratio and hence better spatial resolution increasing the visibility of small cancers. Early reports suggest that the sensitivity and specificity of MRI at 3T for malignant breast lesions increases to 95% and 91% respectively [2]. Moreover, owing to tumour heterogeneity, whole tumour regions of interest (ROIs) may not demonstrate similar enhancement kinetics across the lesion. [1, 8]. With the increasing use of DCE-MRI in breast imaging, automated analysis software and the publication of reproducibility studies, derivation of PK parameters should continue to become more utilised. [7, 9]

MRI sequences:

-We wish to evaluate a new pulse sequence that allows improved temporal and spatial resolution of DCE acquisitions through the use of *k*-space view sharing. A standard DCE breast imaging sequence (VIBRANT, GE Healthcare, Waukesha, WI) has been modified to support the Time Resolved Imaging of Contrast KineticS (TRICKS) *k*-space acquisition strategy previously employed for time-resolved MR angiography[10]. This technique allows a four-fold improvement in temporal resolution (~10-20s), which it is hypothesized will lead to more robust and clinically useful DCE-based imaging metrics for breast tumours.

Accurate PK modelling of the DCE derived contrast agent uptake requires the determination of the baseline T_1 relaxation time of the tissue. This is most effectively obtained using a 3D spoiled gradient echo imaging sequence with multiple flip angles (MFA). Unfortunately, the shorter radiofrequency (RF) wavelengths at 3T means there is significant variation in the RF excitation magnetic field, known as B_1^+. It is therefore necessary to perform a spatial mapping of the B_1^+ field in order to spatially correct the flip angles. We will implement and investigate the use of various B_1^+ mapping methods , such as the Bloch-Siegert method [11]

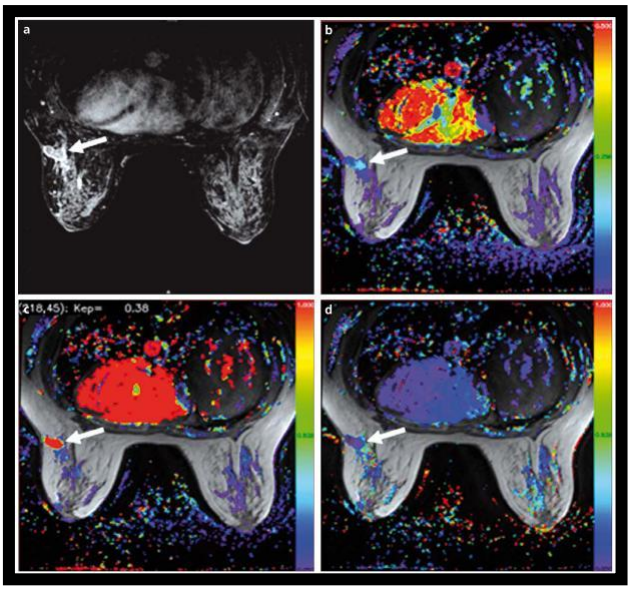

Figure 2: A 43-year-old female with breast cancer. *Axial T1W DCE-MR image demonstrates an enhancing lesion in the left breast (arrow)* ***(a)****. Color-coded* K^{trans} ***(b)****,* K_{ep} ***(c)*** *and* V_e ***(d)*** *maps delineate the tumor (arrows).[6] Courtesy of Turkbey et al, 2010.*

Quantitative image metrics of vascular angiogenesis will be obtained by firstly acquiring B_1^+ maps and MFA gradient echo images. The B_1^+ map data will then be used to correct the quantitative baseline $T1_0$ values. In house software, already developed, will be used to spatially co-register the B_1^+, T_{10} and the DCE acquisitions. The DCE and T_{10} images will then be analysed using a commercial PK analysis package (Jim, Xinapse Systems, Aldwincle, Northamptonshire) to obtain metrics such as IAUGC, K^{trans}, and v_e.

-Logistic regression analysis combining **Magnetisation transfer (MT) imaging** with DCE-MRI has recently been demonstrated to increase the specificity and sensitivity of diagnosing malignancy [8]. MTI exploits the interactions of water protons with the macromolecular environment and aims to distinguish ‘free’ water proton pools and ‘restricted’ protons pools bound to proteins and macromolecules. While these protons are not normally detected in conventional MRI experiments, their presence can be deduced by the way in which such presaturation leads to a reduction in the signal detected from the more mobile protons[12]. Exchange between these two pools gives rise to the MT effect, reported as the magnetization transfer ratio (MTR) which is the ratio of intensities in images acquired with the MT presaturation pulses turned on and off. A preliminary study in breast cancer showed MTR being lower in malignant lesions lower than benign ones, reflecting the greater fibrous content of benign breast lesions[13].

-Blood oxygen level-dependent **(BOLD)** imaging relies on the paramagnetic property of deoxyhaemoglobin for imaging tissue hypoxia; we will investigate changes to autoregulation in response to inhalation of O_2 via intranasal cannula. [14] Tumour cells are known to become hypoxic and fragment, leaving fibrotic and collagenous tissue.[3, 14]

-**Diffusion weighted imaging** provides functional information relating to Brownian motion of water molecules. Diffusion is reduced in tumour tissue due to its high cellular density in respect to fibroglandular tissue.[1, 6] Mean ADC (the apparent diffusion coefficient) is a quantitative diffusion metric which is reduced in malignant lesions than benign and normal breast tissue.[1] We intend to apply an experimental reduced field-of-view DWI imaging sequence, employing 2D RF excitation which has reduced distortion compared to conventional echo planar imaging (EPI) techniques. [15]

-Research geared towards understanding the impact of choline-containing metabolites (tCho) in cell turnover and proliferation on **MRSpectroscopy** as cells transform from the normal state to the malignant form has been demonstrated. Most MRS studies to date have reported an increase in the signal from choline-containing compounds in malignant lesions compared to benign lesions.[16-18] Studies at 1.5T rely on the simple presence or absence of choline signal as the biomarker, but this is confounded by the variability in sensitivity and shimming [17]. Quantification shows promise for increasing the reliability of the measurements due to higher sensitivity at higher field strength. An observer performance study done at 4 T evaluated the use of 1H-MRS findings in addition to DCE-MRI for breast lesion assessment, with sensitivity and specificity reported to be 94% and 57%, respectively.[16, 18]

Histopathology

On histopathology, proliferation indices of the vascular endothelium and that of the tumour tissue will be explored using Ki-67. Mean vascular density will be reported based on CD-34 and CD-31 staining. Quantification of serum and tumour VEGF will be examined to validate the DCE-MRI parameters.

Aim of the project:

Objective:

The principal objective of this pilot study is to examine the use of a prototype acquisition sequence in terms of its ability to distinguish breast lesions on DCE-MR images, enabling pharmacokinetic modelling (K^{trans} and v_e mapping) and assessing its implementation in routine clinical practice.

Hypothesis:

High temporal resolution DCE-MRI research sequences can be used to assess the vascular pharmacokinetic maps of breast tumours non-invasively and correlate with their regional proliferative epitopes of the malignant breast specimens.

Secondary Aims:

-Evaluate the heterogeneity of the pharmacokinetic vascular maps on DCE-MRI and assess reproducibility of the PK modelling using VIBRANT-TRICKS sequence.
-Evaluate how MT relates to the histopathology correlates.
-Examine the ADC map heterogeneity from the reduced FOV sequence and compare to the conventional diffusion weighted sequence.
-Investigate if we can detect changes in BOLD contrast within tumours before and after100 % O_2 inhalation.
-Dependent on the scan time and patient compliance, further sequences e.g.: relation of the MRS choline levels' to the histopathological vascular proliferation maps will be investigated.

Eligibility Criteria:

-Patient Selection:

Inclusion Criteria: All women aged 18 years or older with primary breast cancer whom:

1. Planned treatment will include surgery and/or chemotherapy.
2. Tumours $\geq$ 10 mm in size.

Exclusion criteria include patients who:

1. Unable to provide informed consent/unwilling to participate.
2. Medically unstable.
3. Known contraindications to MRI.
4. Known allergic reactions to Gd contrast agent or poor renal function.
5. Had undergone chemotherapy or hormonal therapy for breast cancer in previous 12 months.
6. Had previous surgery or radiotherapy for cancer to the ipsilateral breast or previous surgery to the ipsilateral breast within the past 4 months for benign breast disease.
7. Had a history of serious breast trauma within the past 3 months.
8. Undergoing MRI for assessment of the integrity of breast implants.

-Sample Size:

In this pilot study, we aim to recruit approximately 255 patients with primary invasive breast cancer and image them prior to management. A cohort of 90 patients will be imaged once prior to surgery to establish a relationship between DCE-MRI

parameters and their respective histopathology markers (cellular density and proliferation markers). (This phase of the study has now ended with a total of **78 recruited patients**).

The second patient cohort undergoing chemotherapy will have 3-4 MR scans during the course of treatment. **37** patients have been recruited for three MRIs (pre-treatment, mid-way through treatment and the end of chemotherapy). This goes in hand with standard clinical breast management to follow up cancer patients during drug therapy. A further **20 patients** have been recruited for an extra post cycle 1 MRI. We anticipate increasing enrolment for the post cycle 1 MRI to include a further **120 patients**. For the purpose of this pilot study, with the main objective of assessing the novel DCE-MRI prototype sequence in providing more accurate information regarding perfusion across the tumour, insufficient information is known with relatively insufficient prior knowledge available to perform a formal sample size calculation. The defined sample size of 255 women was determined based on the recent recruitment rates and higher participation in the study. The study is funded through two bodies: the Cancer Imaging Centre (CIC) and Experimental Cancer Medicine Centre (ECMC) network in September 2013, which can accommodate the increased study population.

-Study Milestone

Start recruitment: March 2013
End recruitment: October 2017

-Patient Recruitment and Consent:

Patients are identified at the breast multi-disciplinary meeting. Patients with breast cancer who are planned to undergo surgery and/or chemotherapy will be approached in the clinic after they are given their core biopsy results and a member of the multi-disciplinary breast team will explain the study to the patient, the nature of the scans and the advantages and disadvantages of participation. Patients will be given a detailed Information Sheet /Informed Consent Form. Patients will be then contacted by the research nurse and asked if they wish to take part in the study.

Dependent on their treatment plans, an appropriate MRI appointment will be booked in the MRIS unit of Addenbookes hospital. If they agree to participate , all MRI appointments will be booked on the 3T scanner.

- Patients undergoing surgery will be asked to have one MRI scan prior to their operation. This will enable correlating the imaging findings with that obtained on the histopathological specimen after the procedure. (This phase of the study has now ended).
- In the case that drug therapy is their first line of treatment, patients will be asked to have up to three MRI scans along their course of therapy as they would in a clinical non-research setting. As standard breast management, this will occur at three intervals; one before the start of therapy, the second mid-way through their treatment and one at the end. As part of the research, patients will be approached for an extra MRI scan early during treatment (ideally after the completion of the first cycle). This will help estimate the

early effect of chemotherapy on the cancer size and behaviour. At all these visits, the new MRI method implemented will provide both the clinical and research information at the same setting. The post cycle 1 MRI will not constitute a separate visit to the hospital, as it will be booked on the same day of their follow-up oncology appointment. All the MRI's will be clinically reported and kept in your medical notes as standard of care. These 3T MRI examinations will then replace the routine clinical breast 1.5T MRI examinations. They will be asked for their informed consent when they arrive for the imaging investigation. The research 3T MRI exam will last no more than 30 minutes. The preparation time before the patient enters the scanner should take no longer than 15 minutes for all breast MR scans. Every effort will be made to minimize the time involved and discomfort of the patient. If a patient is unwilling to participate this does not affect their care in any way.

-Procedure:

Patients will attend the MRIS unit at Addenbrooke's hospital for the research MRI breast examination. The examinations will be conducted using a 3T GE MRI system with a dedicated bilateral phased array breast coil. Premenopausal women will have their MRI studies scheduled in the 2nd week of their menstrual cycle to minimize hormone-related enhancement of benign breast tissue. An intravenous catheter will be inserted into an arm vein for contrast agent administration. For the BOLD imaging, patients will receive 100% O_2 via intranasal cannula or mask for 5 minutes. The patient will be placed in the prone position with both breasts freely suspended within the breast coil with their arms positioned at the sides for the examination. Dedicated software and sequences will be used to generate DCE-MRI, MRS, MT, DWI and BOLD imaging data. The entire scanning process should take less than one hour.

-Image acquisition:

Experimental pulse sequences that provide both high spatial (1.4 mm^3 voxel volume) and temporal resolution (10-20 sec) will be employed by combining a breast optimized T1W sequence with time resolved imaging of contrast kinetics (TRICKS). By incorporating view sharing and temporal interpolation, images of high temporal and spatial resolution can be reconstructed.

Statistical analysis and Results:

The principal hypothesis, exploring the relationship between DCE metrics and histopathology markers, will initially involve performing formal statistical analyses to assess the normality assumptions of each respective distribution. Appropriate univariate statistics will then be performed to express the relationship between each imaging marker (K^{trans} and v_e) and the respective cellular density and proliferation

markers. Forward stepwise multivariate linear regression will then be performed to establish which combination of histopathology markers best relate to the quantitative DCE-MRI metrics.

Secondary aims of the study include investigating if 3D non-rigid registration algorithms improve the repeatability of the quantitative DCE metrics. We will also report the repeatability of MTR, BOLD and DWI as well as investigating how each of these novel sequences relates to the histopathology samples.

The repeatability sub-study will involve recruiting 10 patients who will be imaged twice (approximately 24 hours apart).

-Clinical Assessment and Data Management:

Data collected in the course of the study will be stored and analysed by two radiologists' expert in breast imaging. A comprehensive diagnostic statement evaluating the fat-suppression technique, the morphology and enhancement kinetics of the lesions, quality of examination with particular relation to patient movement (presence of artefacts) and other general comments will be recorded.
Thereafter, normal procedure will be followed as per routine breast MRI including:

1. Correlation of abnormalities with standard imaging.
2. Second –look targeted US of additional disease.
3. MRI-guided biopsy of lesion if it does not become visible on US and lesion affects patient management.

In the event of an additional suspicious lesion found on MRI, a second-look targeted US will be done to localize the abnormality and a core needle biopsy will be taken. Malignant lesions will be excised and treated similar to the primary tumour. For the benign lesions, the US-guided biopsy will be used as the reference.
Findings visible on MRI judged to be less suspicious of malignancy with no potential influence on therapeutic decision will be booked for a second-look targeted US appointment and/or followed up with further imaging as clinically appropriate. Patients with confirmed cancer will proceed to normal standard of care with surgery, neoadjuvant chemotherapy or hormonal therapy.

Study Organisation:

-Administrative Responsibilities

The administrative duties will be undertaken by the supervisor in conjunction with investigator and research staff.

-Patient Withdrawal

The schedule protocol will be discontinued in the following circumstances in which case a 1.5 tesla MRI examination will be re-booked:

- The patient opts to withdraw from the study.

- The patient is inadvertently enrolled without meeting the eligibility criteria, in which case continuation must be agreed with the relevant body.

Ethical and Regulatory Issues:

-Patient Confidentiality

Data and images will be anonymised at source and the patient trial number will be used as a unique identifier. The personal data recorded on radiological images will be regarded as strictly confidential and will be handled and stored accordance with 1998 Data Protection Act.

-Sponsorship

This is an investigator-led local study, which is sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge.

-Results and Publication Policy

Study results will be presented at national and international meetings. Manuscripts will be devised for publication in peer-reviewed scientific journals.

Data may be shared with a range of researchers in the UK, overseas and in the commercial sector for the purposes of academic research and development of new software to better evaluate breast cancer. All personal information (e.g.: name, age, hospital number) will be removed before academic publication and sharing.

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ΜΗΤΕΡΑ
Με ευθύνη για τη ζωή
ΜΕΛΟΣ ΤΟΥ ΟΜΙΛΟΥ ΗΗΓ

ΔΗΛΩΣΗ ΚΑΙ ΣΥΝΑΙΝΕΣΗ ΓΙΑ ΔΙΕΝΕΡΓΕΙΑ ΜΑΓΝΗΤΙΚΗΣ ΤΟΜΟΓΡΑΦΙΑΣ

(Συμπληρώνεται από τον Ασθενή ή και από τον Συνοδό που παρευρίσκεται στον εξεταστικό χώρο του μαγνητικού τομογράφου)

ΧΩΡΟΣ ΕΠΙΚΟΛΛΗΣΗΣ
ΑΥΤΟΚΟΛΛΗΤΗΣ ΕΤΙΚΕΤΑΣ
ΣΤΟΙΧΕΙΩΝ ΑΣΘΕΝΟΥΣ.

Συμπληρώνεται από: **ΑΣΘΕΝΗΣ** ☐ **ΝΟΜΙΜΟΣ-ΟΙ ΑΝΤΙΠΡΟΣΩΠΟΣ-ΟΙ** ☐ **ΣΥΝΟΔΟΣ** ☐

ΣΤΟΙΧΕΙΑ ΑΣΘΕΝΟΥΣ

Επώνυμο: _____ Όνομα: _____ Πατρώνυμο: _____

Ημ/νία Γέννησης: _____ Φύλο: _____ Τηλέφωνο: _____

ΣΤΟΙΧΕΙΑ ΝΟΜΙΜΟΥ/ΩΝ ΑΝΤΙΠΡΟΣΩΠΟΥ/ΩΝ (Απαιτείται η συμπλήρωση των στοιχείων και των 2 γονέων σε περίπτωση ανήλικου)

Ιδιότητα αντιπροσώπου 1:_____ Επώνυμο: _____ Όνομα: _____

Αρ. Δελτίου Ταυτότητας: _____ Τηλέφωνο: _____

Ιδιότητα αντιπροσώπου 2:_____ Επώνυμο: _____ Όνομα: _____

Αρ. Δελτίου Ταυτότητας: _____ Τηλέφωνο: _____

Αιτία ανικανότητας ή αδυναμίας συναίνεσης του ίδιου του ασθενούς:

ΣΤΟΙΧΕΙΑ ΣΥΝΟΔΟΥ (που θα παρευρεθεί στο χώρο του εξεταστικού θαλάμου του Μαγνητικού Τομογράφου την ώρα της εξέτασης)

Επώνυμο: _____Όνομα: _____ Αριθμός Δελτίου Ταυτότητας:_____ Τηλέφωνο:_____

Είδος Εξέτασης:		**Βάρος Σώματος:**	

Σας ενημερώνουμε ότι για τη λήψη εικόνων μαγνητικής τομογραφίας χρησιμοποιείται ένας πολύ ισχυρός μαγνήτης και ραδιοκύματα συχνότητας FM. Λόγω του ισχυρού μαγνήτη, σιδηρομαγνητικά υλικά απαγορεύονται αυστηρώς μέσα στο δωμάτιο που βρίσκεται ο μαγνήτης. Για την ασφάλειά σας, με μία σειρά ερωτήσεων, θα επιβεβαιώσουμε ότι δεν έχετε εμφυτευμένα μεταλλικά αντικείμενα που θα ήταν αντένδειξη για μαγνητική τομογραφία. Μερικά μεταλλικά αντικείμενα δεν αποτελούν αντένδειξη για την εξέταση, αλλά μπορεί να επηρεάσουν την ποιότητα των εικόνων.

Παρακαλούμε απαντήστε στα παρακάτω σημειώνοντας (√) στο αντίστοιχο τετραγωνίδιο τη σωστή απάντηση (ΝΑΙ/ΟΧΙ) και ενημερώστε τη νοσηλεύτρια ή τον τεχνολόγο του τμήματος.
Για τις απορίες σας παρακαλούμε ρωτήστε τη νοσηλεύτρια ή τον τεχνολόγο.

	ΝΑΙ	**ΟΧΙ**
1. Έχετε κάνει χειρουργεία στην καρδιά;	☐	☐
Έχετε βηματοδότη ή επικαρδιακά καλώδια;	☐	☐
Έχετε αγγειακά stents (στεντς) ή κλιπς;	☐	☐
Έχετε καρδιακή προσθετική βαλβίδα;	☐	☐
Έχετε χειρουργικά σύρματα (by pass ή άλλη επέμβαση);	☐	☐
Έχετε καρδιακό απινιδωτή (ICD);	☐	☐
Έχετε εμφυτευμένη μεταλλική αντλία;	☐	☐
2. Έχετε κάνει χειρουργεία στο κεφάλι;	☐	☐
Έχετε κλιπς ανευρύσματος ή σύρμα-κόιλ (coil);	☐	☐
Έχετε βαλβίδα παροχέτευσης υδροκεφάλου;	☐	☐
Έχετε νευροδιεγέρτη, βιοενεργοποιητές ή συσκευές TENS, DBS ηλεκτρόδια;	☐	☐
Έχετε κοιλιακά προθέματα;	☐	☐
Έχετε μέταλλα στα μάτια;	☐	☐
3. Έχετε κάνει χειρουργεία στη σπονδυλική στήλη ή σε άρθρωση;	☐	☐
Έχετε μεταλλικές ράβδους σπονδυλοδεσίας ή σκολίωσης;	☐	☐
Έχετε μεταλλική άρθρωση ή μέταλλα στα οστά;	☐	☐

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	NAI	OXI
4. Έχετε κάνει άλλα χειρουργεία; Εξηγήστε:	☐	☐
Έχετε μεταλλικά προθέματα;	☐	☐
Έχετε γραμμή έγχυσης φαρμάκων (porta cath, hickman);	☐	☐
Έχετε φίλτρο κάτω κοίλης φλέβας, πρόθεμα πέους, διάφραγμα-σπιράλ μήτρας (IUD);	☐	☐
5. Έχετε μεταλλικά προθέματα στις οδοντοστοιχίες;	☐	☐
6. Έχετε σκουλαρίκια στα αυτιά ή αλλού στο σώμα;	☐	☐
7. Έχετε τατουάζ στο σώμα?	☐	☐
8. Έχετε διαδερμικά φαρμακευτικά σκευάσματα (νικοτίνης, νιτρογλυκερίνης, κλπ.);	☐	☐
9. Έχετε άλλο αντικείμενο εμφυτευμένο στο σώμα (κοχλιακό εμφύτευμα ή άλλο);	☐	☐
Αν ναι, παρακαλώ περιγράψτε: _____		
10. Έχετε πρόβλημα νεφρικής λειτουργίας; (Αφορά μόνο τον ασθενή)	☐	☐
Έχετε αυξημένη κρεατινίνη;	☐	☐
Έχετε φλεγμονή, τραύμα ή χειρουργείο στους νεφρούς;	☐	☐
Έχετε υποβληθεί σε θεραπεία σε τεχνητό νεφρό;	☐	☐
11. ΓΙΑ ΓΥΝΑΙΚΕΣ: Υπάρχει πιθανότητα εγκυμοσύνης;	☐	☐
Αν και δεν υπάρχουν επιστημονικά δεδομένα που να αποδεικνύουν κινδύνους – παρενέργειες στο έμβρυο από τη διενέργεια μαγνητικής τομογραφίας σε εγκύους, σύμφωνα με τις οδηγίες της Παγκόσμιας Οργάνωσης Υγείας, η εξέταση αυτή κατά το 1ο τρίμηνο της κύησης θα πρέπει να διενεργείται μόνο όταν υπάρχουν σοβαροί ιατρικοί λόγοι.		
12. ΓΙΑ ΓΥΝΑΙΚΕΣ: Έχετε εμφυτευμένη συσκευή διάτασης στον μαστό;	☐	☐
13. ΓΙΑ ΓΥΝΑΙΚΕΣ: Θηλάζετε; (Αφορά μόνο τον ασθενή)	☐	☐
Αν και είναι αμφίβολο να υπάρχει σημαντική απέκκριση του σκιαγραφικού στο μητρικό γάλα, συστήνεται η διακοπή του θηλασμού για 24 ώρες μετά την εξέταση εφόσον σας χορηγηθεί ενδοφλέβιο σκιαγραφικό.		
14. Έχετε αλλεργία σε φάρμακα ή ουσίες; (Αφορά μόνο τον ασθενή)	☐	☐
Αν ναι, παρακαλώ περιγράψτε: _____		
15. Αν χρειαστεί να συμπληρωθεί η εξέταση με ενδοφλέβιο σκιαγραφικό, συμφωνείτε; (Αφορά μόνο τον ασθενή)	☐	☐

Σας ενημερώνουμε ότι το σκιαγραφικό είναι ένα φάρμακο που χορηγείται όταν χρειάζεται να πάρουμε περισσότερες πληροφορίες από τις εικόνες της εξέτασης. Δεν χορηγείται σε εγκύους. Για ορισμένα άτομα με σοβαρή νεφρική δυσλειτουργία, αναφέρεται κίνδυνος επιπλοκών από τη χορήγηση του. Επίσης, σπάνια αναφέρονται αλλεργικές αντιδράσεις στο σκιαγραφικό.

Παρακαλούμε αφαιρέσετε όλα τα μεταλλικά/μαγνητικά αντικείμενα που φέρετε (πχ. κλειδιά, κέρματα, ρολόγια, πιστωτικές κάρτες, εισιτήρια, τηλέφωνα)

Διάβασα με ηρεμία τα παραπάνω, τα κατανόησα, απάντησα αληθώς, δεν έχω καμία απορία σε όσα αναφέρονται και δηλώνω ότι δίνω ρητά και ανεπιφύλακτα τη συγκατάθεσή μου στον/ στους ιατρό/ούς να προχωρήσουν στη διενέργεια της ως άνω διαγνωστικής πράξης.

Διάβασα με ηρεμία τα παραπάνω, τα κατανόησα, απάντησα αληθώς, δεν έχω καμία απορία σε όσα αναφέρονται και δηλώνω ρητά και ανεπιφύλακτα ότι επιθυμώ να παρευρίσκομαι ως συνοδός στον εξεταστικό θάλαμο την ώρα της εξέτασης.

Ημερομηνία / Ώρα:		**Ασθενής/Συνοδός** (Υπογραφή και Ονοματεπώνυμο):	
Ο Ιατρός / Μέλος του προσωπικού: (Υπογραφή και Ονοματεπώνυμο):		**Ο/Η/Οι νόμιμος-η-οι αντιπρόσωπος-οι** (Υπογραφή και Ονοματεπώνυμο):	1. _____ 2.

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Rasoolzadeh, Nika

From: Rietveld, Thomas on behalf of Postbus Commissie Mensgebonden Onderzoek
Sent: Tuesday, April 9, 2024 4:24 PM
To: Rasoolzadeh, Nika
Subject: 2024-17192 niet-WMO-onderzoek en geen lokale toets

Titel van het onderzoeksprotocol: ODELIA An Open Consortium for Decentralized Medical Artificial Intelligence
Dossiernummer: 2024-17192
Naam hoofdonderzoeker: Dr. R.M. Mann
Naam onderzoekscentrum: Radboudumc
Naam indiener: Nika Rasoolzadeh
Datum indiening: 25-03-2024

Geachte Nika Rasoolzadeh,

U heeft de METC Oost-Nederland verzocht een uitspraak te doen over of bovengenoemd onderzoek onder de Wet medisch-wetenschappelijk onderzoek met mensen (WMO) valt en op grond daarvan door een erkende medisch-ethische toetsingscommissie beoordeeld moet worden.

De onderzoeksdeelnemers worden niet aan WMO-plichtige handelingen onderworpen en aan hen worden geen WMO-plichtige gedragingen opgelegd.

Op grond hiervan verklaart de METC Oost-Nederland dat het onderzoek niet onder de WMO valt. Voor de uitvoering ervan is derhalve geen positief oordeel vereist van de METC Oost-Nederland of een andere erkende medisch-ethische toetsingscommissie.

Het onderzoek is tevens voorgelegd aan CMO Radboudumc (lokale toetsingscommissie voor niet-WMO-onderzoek). De CMO Radboudumc toetst niet-WMO-plichtig onderzoek in de volgende gevallen:

- Het onderzoek brengt de niet-verwaarloosbare kans mee dat nieuwe bevindingen gegeneerd worden over de (toekomstige) gezondheidstoestand van de deelnemers (of hun bloedverwanten).
- Het onderzoek is maatschappelijk controversieel: het bevindt zich op een onderzoeksterrein waarover binnen de samenleving verschillende levensbeschouwelijke of morele opvattingen bestaan ten aanzien van de toelaatbaarheid ervan.

Uw onderzoek valt niet onder een van deze twee toetsingsgronden. Op grond hiervan oordeelt CMO Radboudumc dat voor de uitvoering van uw onderzoek geen oordeel van de CMO Radboudumc vereist is.

De METC Oost-Nederland en CMO Radboudumc hebben uw onderzoek niet onderworpen aan een inhoudelijk oordeel (dit kan daarom niet zo worden vermeld in een proefpersoneninformatie).

Graag attendeer ik u op de wet- en regelgeving m.b.t. niet-WMO-plichtig onderzoek en het beleid van het Radboudumc daaromtrent, te vinden in het Integraal Kwaliteitssysteem wetenschappelijk onderzoek (IKS). Doet u statusonderzoek, dan vindt u in het IKS bijv. de SOP Gebruik van (medische) gegevens, beeld- en lichaamsmateriaal voor niet-WMO-plichtig mensgebonden wetenschappelijk onderzoek. Mocht u vragen hebben over informatie in het IKS dan kunt u e-

mailen naar de Postbus IKS (uw vra(a)g(en) worden dan besproken met ter zake deskundige in het Radboudumc en zij kunnen u dan adviseren).

Ik vertrouw erop u met dit bericht van dienst te zijn. Ik wens u succes met de uitvoering van uw onderzoek.

Met vriendelijke groet,

Dr. Jaap Deinum
Vice-voorzitter METC Oost-Nederland
Voorzitter CMO Radboudumc

CMO Radboudumc
METCoost-en-CMO@radboudumc.nl
T (024) 3613154

Radboud universitair medisch centrum
Tandheelkunde gebouw
Philips van Leydenlaan 25 (route 348), Nijmegen
www.radboudumc.nl

Ontvangen documenten:
- Aanbiedingsbrief d.d. 25 maart 2024
- Onderzoeksprotocol versie 1, d.d. 25 maart 2024

Title: An Open Consortium for Decentralized Medical Artificial Intelligence
Filenumber: 2024-17192

Dear Nika Rasoolzadeh,

Please be informed that the abovementioned study will be carried out in accordance with the applicable legislation such as
- Medical Research involving Human Subjects Act
- Medical Treatment Contracts Act

and review by a research ethics committee.

Best regards,
Dr. Jaap Deinum, vice-chairman

Research Ethics Committee
Radboud University Nijmegen Medical Centre

CMO 2024-17192

ODELIA An Open Consortium for Decentralized Medical Artificial Intelligence

Version	1
Date	25-03-2024
Principal investigator	MD PhD Ritse M. Mann
Sponsor	Radboudumc

1. Rationale

Early detection and treatment play a significant role in reducing the mortality rates of cancer patients. Although current AI technologies cannot replace radiologists, they have proven to provide feasible assistance and insights for detecting and diagnosing cancers compared to traditional methods [1, 2]. Screening, diagnosis, prognosis, risk assessment, and treatment alternatives are some of the areas in which AI can support medical professionals.

Among all types of cancer, breast cancer is the leading cause of death for females globally [3]. Screening mammography is used for mortality prevention, and it has been shown to reduce mortality rates by nearly 40% for women who attend breast cancer screenings [3]. As the most sensitive imaging method for breast cancer detection, MRI can capture cancers at an earlier stage than mammography in all women. It contributes to the enhancement of surgical procedures, reducing re-excisions and avoiding unnecessary mastectomies. Furthermore, it facilitates neoadjuvant chemotherapy patient selection and further modifications of therapeutic agents [4]. However, achieving high diagnostic accuracies with MRI depends significantly on reader expertise. Low specificity and high rates of false-positive diagnoses, often attributed to non-expert reader interpretations, impede the utilization of MRI in cancer screening. Moreover, the expanding volume of imaging data has not been met with a proportional increase in trained specialty radiologists, escalating the evaluation workload. Therefore, the enhancement of AI-based solutions for breast cancer screening is of great importance.

While AI solutions and technologies demonstrate significant potential in pushing boundaries, they are not without limitations. Particularly in the realm of medical imaging, challenges such as data gathering, accessibility, sharing, the complexity of data, and the availability of efficient computational resources for AI systems need to be addressed. Patient confidentiality and privacy concerns for data sharing seek alternative solutions for AI technologies. Swarm Learning (SL) is one of the solutions that can address these challenges by providing model trainings across a decentralized network of devices. Each device processes its data and training locally and communicates with other devices in the network to improve the overall model. SL can establish the foundation for a continuously evolving framework for AI models in the future, enhancing AI systems in the medical field and leading to improved capabilities in early detection, stratification, and treatment of diseases. However, SL in medical AI has never been applied in a real-world large-scale setting.

As an exemplary case study, ODELIA starts with the focus on breast cancer screening with MRI. To address the outlined challenges ODELIA aims to build the first pan-European academic and clinical consortium to develop, implement and evaluate SL-based workflows to train AI models in medical imaging. It will enable a new and more powerful generation of AI models by solving data sharing issues and enabling collaboration, creating a real-world experience in SL. Each partner will independently develop and train an AI model for breast cancer detection using MRI data. The partners will exchange their local training model (in a Docker) for testing on the local test sets at all other institutions. Additionally, every partner will submit a training model via SL. Models will be trained on the combined data contributed by all partners without the need to exchange any data. The algorithms will be evaluated on the hold-out test sets from all partner institutions. The final evaluation will involve comparing all AI models trained on the whole data (via SL) and the performance of each AI model trained only on local data. This task will be performed with ODELIA's SL software in an iterative way. All the codes for the developed open-source SL software are available on GitHub.

2. Objective

The objective is to develop, train and validate our AI algorithm using the dataset of MRI screening study for breast cancer screening tasks.

3. Main study parameters

The database of study with CMO dossier number 2020-6325 is requested in this submission to train clinical AI models locally for breast cancer detection for high performance in real-world settings. The diagnoses of the images (the radiological and pathological reports) are required to generate training labels for each patient without manually delineating a suspected tumor. A structured annotated data will be created locally using a standard ODELIA annotation scheme for a more straightforward performance evaluation. This approach also enables exploring additional medical applications such as classification, molecular subtype prediction, recurrence prediction, and risk assessment. After local testing, the models will be shared with other partners for their evaluation. Similarly, we will test the other partners' models with our local datasets without sharing data. Finally, additional images other than MRI, if already available with no patient identification, can be employed for validation studies.

4. Study design

This study is a retrospective study which reuses care data (=data already acquired for clinical purposes) which are already stored in a database created for the study "MRI Screening", CMO dossier 2umber 2020-6325. Descriptive clinical data has already been coupled to the medical images. This database is a coded database. Researchers without a treatment relationship will neither have access to identifiable data nor to the identification log. The subject identification log is managed by the Trial Office Medical Imaging and stored at PIMS 191 keyfile. The following people have access to the subject identification log: Lian Pennings from the Trial Office Medical Imaging.

The database will be supplemented with additional images, radiological and pathological reports of the patients within the database, when available.

Data stored in PACS will be retrieved via the Medical Imaging's de-identification software.

Radiology reports will be retrieved by the DIAG research group. The identifiable information will be removed from the data by DIAG.
Under the following conditions the researcher can ask the care provider and/or data manager to release identifiable data: Discrepancies or mistakes observed in the coupled data which can affect the training of the AI model and result evaluations.

5. Study population

All patients included in “MRI Screening” study with an estimate sample size of 3391 will be used for both training and validation.
The database consist of data from:

- Patients registered at the Radboudumc
- Patients who participated in hospital based breast screening between 2003 and 2020
- Patients who had breast screening by MRI or by MRI and mammography

6. Handling and storage of data and documents

All data and documents used in this study are digitally stored at Radboudumc breast archive and servers.

7. Data sharing

A completely anonymized subset of the database of “MRI Screening” will be shared publicly as part of an online challenge. The subset will be selected under Trial Office Medical Imaging supervision and approval. It will contain MRI images and coupled clinical information. The participants who enter the challenge will need to make a request for access to the data. After the evaluation of the request to the research team the subset will be shared with the participants.

8. References

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Dictamen Protocolo Favorable

C.P. HORIZON-HLTH-2021-CARE-05-02
C.I. 23/430-E

23 de julio de 2023

Dra. Mar García Arenillas
Presidenta del CEIm Hospital Clínico San Carlos

CERTIFICA

- Que el CEIm Hospital Clínico San Carlos en reunión de Comisión Permanente, acta 8.1/23, ha evaluado la respuesta a las aclaraciones solicitadas con anterioridad al estudio:

Título: ***ODELIA - AN OPEN CONSORTIUM FOR DECENTRALIZED MEDICAL ARTIFICIAL INTELLIGENCE.***
ODELIA - UN CONSORCIO ABIERTO PARA LA INTELIGENCIA ARTIFICIAL MÉDICA DESCENTRALIZADA.

Promotor: **FUNDACION RIBERA SALUD**
Investigadora principal: **JULIA CAMPS HERRERO**
Código Promotor: **HORIZON-HLTH-2021-CARE-05-02**
Código Interno: **23/430-E**

Tipo Documento	Versión
Protocolo	Versión 2.0_Julio2023

- Que en este estudio:
  - Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
  - La capacidad del equipo investigador y los medios disponibles son adecuados para llevar a cabo el estudio.
  - El alcance de las compensaciones económicas previstas no interfiere con el respeto de los postulados éticos.
  - Se cumplen los preceptos éticos formulados en la Declaración de Helsinki de la Asociación Médica mundial sobre principios éticos para las investigaciones médicas en seres humanos y en sus posteriores revisiones, así como aquellos exigidos por la normativa legal aplicable en función de las características del estudio.

- Que este Comité ha decidido emitir un **DICTAMEN FAVORABLE**.

- Que en dicha reunión se cumplieron los requisitos establecidos en la legislación vigente – Real Decreto 1090/2015 – para que la decisión del citado CEIm sea válida.

- Que el CEIm Hospital Clínico San Carlos tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm Hospital Clínico San Carlos es la indicada a continuación, teniendo en cuenta que en el caso de que algún miembro participe en el proyecto o declare algún conflicto de interés no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del proyecto.

Presidenta	**Dra. M. García Arenillas**	Esp. Farmacología Clínica
Vicepresidente	**Dr. A. Marcos Dolado**	Esp. Neurología
Secretaria Técnica	**Dra. L. Cabrera García**	Esp. Farmacología Clínica
Vocales	**Dr. M. Carnero Alcazar**	Esp. Cirugía Cardiovascular
	Dr. J.A. García Sáenz	Esp. Oncología Médica
	Dr. F.J. Martín Sánchez	Esp. Urgencias
	Dr. A.M. Molino González	Esp. Medicina Interna
	Dª. M.L. Pastor Alfonso	Otras No Sanitarias
	Dª. M. Peláez Agudo	Atención Primaria
	Dª. T. Peña Rollán	Ldo. Derecho
	Dª. M. Sáenz de Tejada López	Farmacia
	Dª. I. Serrano García	Otras No Sanitarias (Exp. Estadística)
	D. S. Varga Vázquez	Enfermería
	Dr. C. Verdejo Bravo	Esp. Geriatría

Para que conste donde proceda, y a petición del promotor.

Lo que firmo en Madrid, a 20 de julio de 2023

GARCIA ARENILLAS MARIA DEL MAR - 05250249Q

Firmado digitalmente por GARCIA ARENILLAS MARIA DEL MAR - 05250249Q
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Fdo.: Dra. Mar García Arenillas
Presidenta del CEIm Hospital Clínico San Carlos

Participant Recruitment and Data Management in the ODELIA project

Participant Recruitment

Participants for this study on breast cancer detection using MRI imaging will be retrospectively identified from existing clinical and imaging datasets at two Ribera Group hospitals: Hospital Universitario del Vinalopó and Hospital Universitario de Torrejón

These datasets include individuals who underwent breast MRI scans for

- High and intermediate risk screening
- Pre-operative local staging
- Problem solving
- Follow-up of patients with high risk B3 lesions
- Surveillance of breast cancer

performed between 2019 and 2022. Recruitment will be based solely on pre-existing records; no active patient enrollment or additional imaging will be required. All data used will comply with institutional and ethical guidelines for secondary data usage, ensuring that only necessary and de-identified information is accessed for the study.

Data Collection and Storage

Breast MRI scans and clinical data will be collected at Hospital Universitario del Vinalopó in Elche (Alicante) and Hospital Universitario de Torrejón in Torrejón de Ardoz (Madrid) and stored in the Ribera Salud server. The collection and processing of image data from study participants will be limited to the data necessary to achieve the study's objectives.

The extracted data will include imaging in the Digital Imaging and Communications in Medicine (DICOM) format and essential clinical parameters, such as patient demographics, medical history, and breast cancer diagnosis outcomes.

All personal identifiers will be removed during data processing. A secure alphanumeric code will replace identifying information to ensure participant anonymity. The linkage between these codes and patient identities will remain encrypted and stored only at the originating clinical center, accessible exclusively by the local investigator.

The ODELIA research group at RSH will take all necessary precautions to ensure data confidentiality and compliance with European and National data protection

regulations, as well as ICH-GCP standards. Technical and organizational measures will be in place to protect personal data from unauthorized access, disclosure, accidental loss, or alteration. The research team at the Ribera Salud Group will maintain the confidentiality of subjects by assigning them alphanumeric codes. The link between these codes and actual personal data will be securely stored at the clinical center, with access restricted to the local investigator. Source data will be retained for 5 years after publication in a peer-reviewed journal and will be available for inspection by authorized personnel, including the Chief/Principal Investigators, Study Coordinator, and Statistician. Source documents will be accessible for monitoring and audit purposes by the Ethics and Research and Development departments and regulatory bodies upon request.

Data Format

Clinical demographics and outcomes will be collected with a focus on patient privacy.

Ethical Considerations

The study design prioritizes patient confidentiality and adheres to ethical standards for data handling and secondary usage. All procedures for data collection, storage, and processing have been reviewed and approved by institutional ethics boards. Participants' anonymity will be rigorously maintained, and their data will be used solely for the stated research purposes.

CAMPS HERRERO JULIA MARGARITA - 21637800K

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Gezondheidsraad

Wet bevolkingsonderzoek: aanvullende MRI screening bij vrouwen met hoge borstdensiteit

Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Volksgezondheid, Welzijn en Sport

Onderwerp : Aanbieding advies *Wet bevolkingsonderzoek: aanvullende MRI screening bij vrouwen met hoge borstdensiteit*
Uw kenmerk : PG/OGZ 3042280
Ons kenmerk : I-706-10/ML/bp/272-J12
Bijlagen : 1
Datum : 28 september 2011

Geachte minister,

Op 24 december 2010 vroeg u in het kader van de Wet op het bevolkingsonderzoek (WBO) de Gezondheidsraad advies over een vergunningaanvraag van het Julius Centrum te Utrecht. De aanvraag betreft een onderzoek naar een aanvullende methode van borstonderzoek, door middel van MRI, bij vrouwen uit een specifieke risicogroep, namelijk vrouwen met een zeer hoge dichtheid van het borstweefsel, in de leeftijd van 50 tot 75 jaar.

Hierbij ontvangt u het advies dat is opgesteld door de Commissie WBO van de Gezondheidsraad. De commissie staat positief tegenover het voorgestelde onderzoek en adviseert u om het Julius Centrum vergunning te verlenen om dit onderzoek uit te voeren. Ik onderschrijf het advies van de commissie.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 66 93
E-mail: mfm.langelaar@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

Wet bevolkingsonderzoek: aanvullende MRI screening bij vrouwen met hoge borstdensiteit

aan:

de minister van Volksgezondheid, Welzijn en Sport

Nr. 2011/19, Den Haag, 28 september 2011

De Gezondheidsraad, ingesteld in 1902, is een adviesorgaan met als taak de regering en het parlement ‘voor te lichten over de stand der wetenschap ten aanzien van vraagstukken op het gebied van de volksgezondheid en het gezondheids-(zorg)onderzoek’ (art. 22 Gezondheidswet).

De Gezondheidsraad ontvangt de meeste adviesvragen van de bewindslieden van Volksgezondheid, Welzijn & Sport; Volkshuisvesting, Ruimtelijke Ordening & Milieubeheer; Sociale Zaken & Werkgelegenheid, Landbouw, Natuur & Voedselkwaliteit en Onderwijs, Cultuur & Wetenschap. De raad kan ook op eigen initiatief adviezen uitbrengen, en ontwikkelingen of trends signaleren die van belang zijn voor het overheidsbeleid.

De adviezen van de Gezondheidsraad zijn openbaar en worden als regel opgesteld door multidisciplinaire commissies van – op persoonlijke titel benoemde – Nederlandse en soms buitenlandse deskundigen.

De Gezondheidsraad is lid van het European Science Advisory Network for Health (EuSANH), een Europees netwerk van wetenschappelijke adviesorganen.

De Gezondheidsraad is lid van het International Network of Agencies for Health Technology Assessment (INAHTA), een internationaal samenwerkingsverband van organisaties die zich bezig houden met *health technology assessment*.

INAHTA

U kunt het advies downloaden van www.gr.nl.

Deze publicatie kan als volgt worden aangehaald:
Gezondheidsraad. Wet bevolkingsonderzoek: aanvullende MRI screening bij vrouwen met hoge borstdensiteit. Den Haag: Gezondheidsraad, 2011; publicatienr. 2011/19.

ISBN: 978-90-5549-862-8

Inhoud

Samenvatting

Dit advies betreft een vergunningaanvraag voor een wetenschappelijk onderzoek binnen het bevolkingsonderzoek borstkanker. Doel van het onderzoek is om vast te stellen of een aanvullende MRI-scan meerwaarde heeft bij het detecteren van borstkanker bij vrouwen met hoge borstdensiteit. Aanvrager is het Julius Centrum van het Universitair Medisch Centrum Utrecht. De minister van Volksgezondheid, Welzijn en Sport (VWS) heeft de Gezondheidsraad op 24 december 2010 gevraagd de vergunningaanvraag te toetsen aan de criteria van de Wet op het bevolkingsonderzoek (WBO). Daartoe heeft de Commissie WBO van de raad gekeken naar de wetenschappelijke deugdelijkheid van het onderzoeksvoorstel, de overeenstemming met de wettelijke regels voor medisch handelen, nut en risico van het onderzoek en het belang voor de volksgezondheid.

Het voorgenomen onderzoek

Vrouwen met een hoge borstdensiteit (relatief veel klier- en bindweefsel) hebben meer kans op borstkanker. Bovendien wordt een tumor makkelijker gemist, omdat de tumor in het dichtere borstweefsel op het mammogram minder goed opvalt. Biedt aanvullende MRI voor deze vrouwen uitkomst? De studie selecteert in het reguliere bevolkingsonderzoek vrouwen die op het mammogram geen afwijkingen hebben en een borstdensiteit van 75% of meer. Door het lot bepaald worden 7.237 vrouwen uitgenodigd voor aanvullende MRI (interventiegroep). Vier keer zoveel (28.948) vrouwen vormen de controlegroep, die alleen gevolgd

worden via de kankerregistratie. Na drie screeningsrondes wordt gekeken in hoeverre het aantal intervaltumoren in de interventiegroep lager is dan in de controlegroep. Intervaltumoren zijn tumoren die buiten de screening om ontdekt worden en dat overkomt in Nederland nu ongeveer twee op de duizend gescreende vrouwen.

Wetenschappelijke deugdelijkheid

De commissie oordeelt positief over de wetenschappelijke deugdelijkheid van de aanvraag. De vooronderstelling dat aanvullende MRI voor vrouwen met hoge borstdensiteit van meerwaarde kan zijn is wetenschappelijk voldoende onderbouwd. De opzet is goed, het aantal benodigde deelneemsters is voldoende onderbouwd en de verwachte uitkomst is kwantificeerbaar en toetsbaar.

Overeenstemming met de wettelijke regels voor medisch handelen

De werving van en informatievoorziening aan de beoogde deelneemsters aan het onderzoek voldoen aan de wettelijke criteria. Weliswaar wordt na prerandomisatie alleen de interventiegroep nader geïnformeerd en om schriftelijke toestemming gevraagd, maar de redenen daarvoor en de onderbouwing daarvan zijn volgens de commissie in overeenstemming met de bedoeling van de WBO. Ethisch kan het correcter zijn toestemming te vragen voorafgaand aan de loting, omdat dit als deel van het onderzoek kan worden gezien. Door eerst te loten, zogenoemd prerandomisatie, kan in deze studie worden voorkomen dat de vrouwen met hoge borstdensiteit in de controlegroep ongerust worden en uit eigen beweging vervolgonderzoek gaan aanvragen. Zolang deze studie niet is voltooid met een positief resultaat zou dat onterecht zijn en daarom in strijd zijn met de bedoeling van de WBO. Daarnaast zou het daardoor moeilijker zijn om de resultaten wetenschappelijk te beoordelen. Prerandomisatie kan toelaatbaar zijn als is voldaan aan drie criteria: de studie moet nieuwe inzichten opleveren, die inzichten moeten zonder prerandomisatie in gevaar komen (subsidiariteit) en de studie moet voldoen aan het vereiste van proportionaliteit. Volgens de commissie voldoet prerandomisatie in deze studie voldoende aan deze criteria. Nieuwe inzichten worden verkregen en komen zonder prerandomisatie in gevaar. De controlegroep hoeft geen extra handelingen te ondergaan en ondervindt geen nadeel door niet te weten van het onderzoek.

Nut en risico van het onderzoek

De commissie meent dat nut en risico zich voor de deelnemende vrouwen positief verhouden. De vrouwen kunnen direct profijt hebben van de aanvullende MRI als een tumor wordt gevonden die op het mammogram was gemist. Als er niets wordt gevonden op de MRI worden de vrouwen gerustgesteld en is mogelijk de kans op intervaltumoren lager. De deelnemende vrouwen worden voldoende op de hoogte gesteld van de mogelijke risico's van het onderzoek en er wordt voldoende aandacht besteed aan het beperken van foutpositieve uitslagen.

Belang voor de volksgezondheid

Het betreft een onderzoek naar een aantoonbare risicogroep binnen de screening op borstkanker en daarmee is het volgens de commissie een serieus volksgezondheidsprobleem. Als het onderzoek aantoont dat aanvullende MRI meerwaarde heeft voor deze vrouwen en de kosteneffectiviteitanalyse gunstig uitvalt, levert het onderzoek handvaten om het bevolkingsonderzoek naar borstkanker te verbeteren. Ook een negatieve uitslag van de studie is waardevol: dan is aangetoond dat aanvullende MRI voor deze vrouwen niet nuttig is in het bevolkingsonderzoek.

Conclusie en advies

De aanvraag voldoet volgens de commissie aan de wettelijke criteria van de WBO. De commissie adviseert de minister van VWS vergunning te verlenen voor de uitvoering van dit onderzoek.

Executive summary

Health Council of the Netherlands. Population Screening Act: additional MRI scan for women with high breast density. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/19

This advisory report relates to an application for authorisation for a scientific study within the breast cancer population screening programme. The goal of the study is to determine whether an additional MRI scan has added value for detecting breast cancer in women with high breast density. The applicant is the Julius Center of the University Medical Center Utrecht. On 24 December 2010, the Minister of Health, Welfare and Sport asked the Health Council of the Netherlands to assess the application based on the criteria outlined in the Population Screening Act (WBO). To this end, the Council's WBO Committee examined the scientific integrity of the research proposal, accordance with legal rules for medical actions, the usefulness and risks of the study and the importance to public health.

The planned study

Women with high breast density (a relatively large amount of glandular and connective tissue) run a higher risk of breast cancer. Furthermore, tumours are more easily missed, as the tumour is less apparent on the mammogram due to the denser breast tissue. Is an additional MRI scan a solution for these women? The study selects women from the standard population screening study who have a mammogram without abnormalities and breast density greater than or equal to 75%. 7,237 women will be randomly selected and invited to undergo an additional MRI (intervention group). Four times as many women (28,948) form the

control, and will only be monitored via the cancer registry. After three rounds of screening, the drop in the number of interval tumours in the intervention group compared with the control group will be evaluated. Interval tumours are tumours discovered outside of the screening programme, this currently happens to about two in every thousand screened women in The Netherlands.

Scientific integrity

The Committee rules positively on the scientific integrity of the application. The assumption that additional MRI may have added value for women with high breast density is sufficiently scientifically substantiated. The study design is good, the required number of participants is sufficiently substantiated and the expected outcome quantifiable and testable.

Accordance with legal rules for medical actions

Recruitment and information provision to the intended participants in the study meet legally defined criteria. Although only the intervention group is informed in greater detail and asked for written consent after pre-randomisation, the reasons and substantiation for this choice are, in the opinion of the Committee, in accordance with the intent of the Population Screening Act (WBO). In ethical terms, it may be better to ask for consent prior to randomisation, as this may be seen as part of the study. By randomising first, so-called pre-randomisation, this study can avoid women with high breast density in the control group becoming worried and requesting follow-up testing on their own accord. Until such time as this study is completed and yields a positive result, such testing would be unjustified and in disagreement with the intent of the Population Screening Act (WBO). Additionally, it would make scientific assessment of the results more difficult. Pre-randomisation is admissible if three criteria are met: the study must deliver new insights, these insights must be endangered without pre-randomisation (subsidiarity) and the study must meet the proportionality requirement. According to the Committee, pre-randomisation in this study meets these criteria sufficiently. New insights are obtained and are endangered without pre-randomisation. The control group is not subjected to additional interventions and is not disadvantaged by not knowing about the study.

Usefulness and risks of the study

The Committee believes the balance of usefulness and risks to participating women is positive. The women may profit directly from the additional MRI if a tumour is found that was missed on the mammogram. If the MRI finds nothing, women will be reassured, and the risk of interval tumours may be lower. Participating women are informed sufficiently of the potential risks of the study, and enough attention is given to the discussion of false-positive results.

Importance to public health

This is a study in an identifiable high-risk group within the breast cancer population screening programme, and is therefore, in the opinion of the Committee, a serious public health problem. If the study demonstrates additional MRI has added value for these women, and cost-effectiveness analysis outcomes are positive, the study will provide means for improving breast cancer population screening. A negative study result is also valuable: this will show that additional MRI is not a useful addition to the population screening programme for these women.

Conclusion and recommendations

In the opinion of the Committee, the application meets the legal criteria outlined in the Population Screening Act (WBO). The Committee recommends that the Minister of Health, Welfare and Sport authorise this study.

Hoofdstuk **1**

Inleiding

Borstkanker is een ziekte met een grote ziektelast. Ongeveer één op de zeven Nederlandse vrouwen ontwikkelt gedurende haar leven borstkanker. In 2008 stierven 3.357 vrouwen aan de gevolgen ervan (www.ikcnet.nl). De incidentie stijgt nog steeds. In Nederland is vanaf 1989 begonnen met de implementatie van landelijk bevolkingsonderzoek naar borstkanker met mammografie (röntgenfoto's van de borst), eerst voor vrouwen van 50 tot en met 69 jaar en vanaf 1998 ook voor vrouwen van 70 tot 75 jaar.

Aan het bevolkingsonderzoek borstkanker doen ongeveer 900.000 vrouwen per jaar mee. Bij ongeveer zes op de duizend gescreende vrouwen wordt borstkanker vastgesteld. Screening met behulp van mammografie vertoont een aantal zwakke punten. Zo is bekend dat een aantal tumoren niet ontdekt wordt, leidend tot zogenoemde 'intervaltumoren'. Dit zijn tumoren die buiten de reguliere screening om – in het interval tussen twee opeenvolgende screeningsrondes – ontdekt worden. Intervaltumoren worden bijvoorbeeld gevonden doordat een vrouw klachten krijgt, terwijl de screening een gunstige ('negatieve') uitslag had. Dit geldt voor ongeveer twee vrouwen per duizend deelneemsters. Latere ontdekking van borsttumoren, zoals bij deze intervaltumoren, verkleint de kans op succesvolle therapie. Verder is de specificiteit van mammografie in het bevolkingsonderzoek hoog, maar de positief voorspellende waarde van een positief mammogram vrij laag omdat borstkanker relatief zeldzaam is onder vrouwen vermeend zonder klachten of symptomen. Van elke tien vrouwen waar tijdens de screening iets verdachts wordt gezien zal dit bij zeven vrouwen foutpositief blij-

ken te zijn. Foutpositief wil zeggen dat er uiteindelijk geen borstkanker of voorstadium daarvan gevonden wordt. Nieuwe technieken bieden kansen om de screening te verbeteren, dat wil zeggen meer vrouwen met borstkanker te vinden en/of foutpositieven te voorkómen. Parallel daaraan groeit het besef van de mogelijke voordelen van een bevolkingsonderzoek dat meer op maat gesneden is, dat wil zeggen niet voor iedere vrouw ongeacht haar achtergrond hetzelfde. [1,2] Voordat nieuwe methoden geïmplementeerd kunnen worden in het landelijke bevolkingsonderzoek, moet eerst deugdelijk de effectiviteit, validiteit en veiligheid zijn aangetoond.

In dit advies gaat het over een van de risicofactoren voor het ontwikkelen van borstkanker die een dergelijke meer individuele benadering mogelijk aantrekkelijk maakt. Het Julius Centrum van het Universitair Medisch Centrum Utrecht heeft bij de minister van VWS een vergunningaanvraag voor een wetenschappelijk onderzoek ingediend met als doel om binnen het huidige bevolkingsonderzoek naar borstkanker te onderzoeken wat de meerwaarde kan zijn van MRI voor vrouwen met een hoge borstdensiteit.

1.1 Context

Een belangrijke risicofactor voor het ontwikkelen van borstkanker is het hebben van dicht (in het Engels *dense*) borstweefsel. Bij *dense* borstweefsel is relatief veel fibroglandulairweefsel (klier- en bindweefsel) aanwezig en relatief weinig vetweefsel. Met het percentage klier- en bindweefsel ten opzichte van vet wordt de mate van borstdensiteit uitgedrukt. Een hoge borstdensiteit is een risicofactor onafhankelijk van andere bekende risicofactoren. Body mass index (BMI) en leeftijd kunnen de relatie verstoren, omdat de verhouding tussen klier- en vetweefsel afhankelijk is van deze factoren. Bij vrouwen met een hoge BMI is relatief meer vet in de borsten, waardoor de densiteit lager zou kunnen lijken. Met het stijgen van de leeftijd, zeker na de overgang, daalt de densiteit. Voor de overgang wordt de densiteit mede beïnvloed door de hormonale status. Door te corrigeren voor BMI en leeftijd wordt de relatie tussen densiteit en borstkanker nog duidelijker.[3]

In dit advies wordt een borstdensiteit van 75% of meer als hoge densiteit aangeduid, dat betreft één op de twintig vrouwen. Ten eerste is voor deze vrouwen de kans groter dat ze borstkanker ontwikkelen. Zij hebben een vier tot vijf maal grotere kans op het ontwikkelen van borstkanker dan vrouwen met een lage borstdensiteit van 10% of lager.[4] Ongeveer 80% van de vrouwen heeft echter een gemiddelde borstdensiteit en ten opzichte van deze vrouwen is de kans op het ontwikkelen van borstkanker ruim twee keer hoger.[5] Een densiteit van 50% of

meer is verantwoordelijk voor ongeveer een derde van alle gevallen van borstkanker.[6] Volgens Amerikaans onderzoek wordt bij vrouwen met een leeftijd tot 56 jaar de helft van de intervaltumoren, binnen twaalf maanden na negatieve mammografie, gevonden bij vrouwen met een densiteit van 50% of meer.[6] Als de diagnoses borstkanker per duizend screeningsonderzoeken worden uitgesplitst naar densiteit, dan geldt dat in totaal acht keer de diagnose borstkanker wordt gesteld per duizend screeningsonderzoeken bij vrouwen met een borstdensiteit van 75% of meer (tabel 1), waarvan 55% (ofwel 4,4 per duizend) een intervaltumor is. Zoals hiervoor beschreven zijn die getallen gemiddeld voor alle vrouwen ongeveer zes en twee per duizend.

Ten tweede is voor vrouwen met hoge borstdensiteit de gevoeligheid (sensitiviteit) van mammografie om borstkanker te ontdekken lager dan gemiddeld. Men vermoedt dat dit niet zozeer komt door dat tumoren in borsten met hogere densiteit sneller groeien, maar vooral doordat klier- en bindweefsel röntgenologisch veel nadrukkelijker worden afgebeeld dan vetweefsel en daarmee eventuele afwijkingen versluiert. Frequenter screenen met mammografie zal dan geen afdoende methode zijn om het aantal intervaltumoren te verlagen. Dan is immers de kans dat de tumor op een herhaalde foto wederom gemist wordt net zo groot.[6]

Tabel 1 Verdeling van het aantal borstkankerdiagnoses naar borstdensiteit en verdeling van borstdensiteit over vrouwen van 40-70 jaar.

Borstdensiteit op het mammogram	Aantal borstkankerdiagnoses (screening+interval) per 1000 onderzoeken[a]	Percentage vrouwen[b]
<10%	5,6	27%
10 - 25%	2,5	24%
25 - 50%	5,6	28%
50 - 75%	7,6	14%
>75%	8,0	6%
Totaal	6,2[c]	100%

[a] De verhouding tussen densiteitscategorieën en aantal borstkankerdiagnoses zoals die beschreven is door Kerlikowske e.a.[7] voor vrouwen in de leeftijd 50-69 jaar.

[b] Het percentage vrouwen met een bepaalde borstdensiteit is afgeleid uit een studie van Boyd, hierin zijn data uit drie grote studies naar borstkanker onder vrouwen variërend in leeftijd van 40 tot 70 jaar verdisconteerd.[6]

[c] Het totaal aantal diagnoses is afkomstig uit het rapport Landelijke Evaluatie van bevolkingsonderzoek naar borstkanker in Nederland.[8]

1.1.1 *Magnetic resonance imaging*

Magnetic resonance imaging (MRI) is een techniek die op een andere manier weefsels in beeld brengt.* Hiervoor is geen ioniserende straling nodig en het heeft ook niet het genoemde nadeel van röntgenonderzoek bij verhoogde densiteit. Het toegevoegde nut van MRI boven röntgen is aangetoond voor de detectie van borsttumoren ontstaan in relatie tot andere risicofactoren als bijvoorbeeld dragerschap van het BRCA-gen, maar nog niet in het reguliere bevolkingsonderzoek naar borstkanker.[9]

1.2 Vergunningaanvraag

Op 24 december 2010 heeft de minister van Volksgezondheid, Welzijn en Sport (VWS), in het kader van de Wet op het bevolkingsonderzoek (WBO), de Gezondheidsraad advies gevraagd over een vergunningaanvraag van het Julius Centrum van het Universitair Medisch Centrum Utrecht. De vergunningaanvraag betreft een wetenschappelijk onderzoek naar de meewaarde van aanvullende MRI voor vrouwen in het reguliere bevolkingsonderzoek naar borstkanker (leeftijd van 50 tot 75 jaar) met hoge borstdensiteit maar zonder afwijkingen op het mammogram die kunnen duiden op borstkanker (‘negatief’).

1.3 Wet op het bevolkingsonderzoek

De WBO trad op 1 juli 1996 in werking en is bedoeld om mensen te beschermen tegen bevolkingsonderzoeken die een gevaar kunnen vormen voor de gezondheid; de wet voorziet daarom in een vergunningstelsel. Dit betekent dat bepaalde categorieën bevolkingsonderzoek verboden zijn zonder vergunning van de minister (artikel 3, eerste lid, WBO). De minister moet de Gezondheidsraad horen alvorens te beslissen over vergunningverlening (artikel 6 en artikel 9, derde lid). De voorzitter van de Gezondheidsraad heeft hiervoor een aparte commissie ingesteld: de Commissie WBO in (bijlage A), hierna te noemen: de commissie.

De WBO is alleen van toepassing op ‘bevolkingsonderzoek’, in de wet (artikel 1, onder c) gedefinieerd als:

* Waar in dit advies gesproken wordt van beeldvorming met mammografie, wordt röntgenfotografie van de borsten bedoeld. De beeldvorming met MRI wordt kortweg MRI genoemd.

Geneeskundig onderzoek van personen dat wordt verricht ter uitvoering van een aan de gehele bevolking of aan een categorie daarvan gedaan aanbod dat gericht is op het ten behoeve of mede ten behoeve van de te onderzoeken personen opsporen van ziekten van een bepaalde aard of van bepaalde risico-indicatoren.

De WBO heeft pas gevolgen als het gaat om vergunningplichtig bevolkingsonderzoek, in de wet (artikel 2, eerste lid, WBO) gedefinieerd als:

Bevolkingsonderzoek waarbij gebruik wordt gemaakt van ioniserende straling, bevolkingsonderzoek naar kanker en bevolkingsonderzoek naar ernstige ziekten of afwijkingen waarvoor geen behandeling mogelijk is.

Een vergunning wordt geweigerd (artikel 7, eerste en tweede lid, WBO) als:

- het bevolkingsonderzoek naar wetenschappelijke maatstaven ondeugdelijk is
- of het bevolkingsonderzoek niet in overeenstemming is met wettelijke regels voor medisch handelen
- of het te verwachten nut van het bevolkingsonderzoek niet opweegt tegen de risico's voor de gezondheid van de te onderzoeken personen.

Bovendien kan bij bevolkingsonderzoek dat tevens wetenschappelijk onderzoek is (artikel 3, derde lid, WBO), een vergunning worden geweigerd 'indien het belang van de volksgezondheid een dergelijk onderzoek niet vordert' (artikel 7, tweede lid).

1.4 Toetsing vergunningplicht

Het in de vergunningaanvraag beschreven onderzoeksproject, dat een uitbreiding vormt op het standaard bevolkingsonderzoek naar borstkanker, moet volgens de commissie worden getypeerd als bevolkingsonderzoek in de zin van de WBO. In de eerste plaats is er sprake van 'aanbod' zoals bedoeld in artikel 1, onder c: vrouwen zonder bekende klachten of symptomen worden uitgenodigd voor bevolkingonderzoek. Dit bevolkingsonderzoek is 'mede ten behoeve van de te onderzoeken personen', want de deelneemsters krijgen onderzoeksresultaten en adviezen te horen en zo nodig volgt behandeling.

Dit bevolkingsonderzoek is vergunningplichtig, want het is gericht op borstkanker en er wordt ioniserende straling gebruikt voor de mammografie. Dit vergunningplichtig bevolkingsonderzoek betreft tevens wetenschappelijk onderzoek zoals bedoeld in de WBO (artikel 3, derde lid): er wordt een aanvullende methode van screening aangeboden, waarvoor de vrouwen onderzoek middels

MRI moeten ondergaan. Er is een lopende vergunning voor bevolkingsonderzoek naar borstkanker, maar de bestaande vergunning voorziet niet in aanvullende screening. Daarom is voor dit onderzoek een aparte vergunning vereist.

1.5 Leeswijzer

Hoofdstuk 2 beschrijft de onderzoeksopzet, waarna de aanvraag in hoofdstuk 3 wordt getoetst aan de wettelijke criteria voor vergunningverlening. In hoofdstuk 4 sluit de commissie af met een conclusie en een advies aan de minister van VWS.

Hoofdstuk 2

Onderzoeksvoorstel

2.1 De onderzoeksvragen

De hypothese van de aanvrager is dat door de aanvullende MRI voor vrouwen die deelnemen aan het reguliere bevolkingsonderzoek naar borstkanker die een negatief mammogram hebben en een hoge borstdensiteit (75% of meer) het aantal intervaltumoren, als maat voor een vergrote kans op sterfte ten gevolge van borstkanker, verlaagd kan worden.

Naar aanleiding van die hypothese is de hoofdvraag van het onderzoek: wat is de effectiviteit van tweejaarlijkse mammografie screening aangevuld met MRI in het terugbrengen van het aantal intervaltumoren bij vrouwen met hoge borstdensiteit in vergelijking met alleen mammografie?

Als secundaire onderzoeksvragen aansluitend op de hoofdvraag beschrijft de aanvrager nog drie vragen:

1 Wat is de kosteneffectiviteit van deze strategie?
2 Wat is de invloed van de aanvullende MRI op de kwaliteit van leven?
3 Wat is de deelnamegraad aan de aanvullende MRI?

2.2 De opzet van het wetenschappelijk onderzoek

De onderzoekspopulatie betreft de subgroep van vrouwen met zeer hoge densiteit van het borstweefsel uit de groep vrouwen in de leeftijd van 50 tot 75 jaar, die voor het reguliere borstkankerscreeningsprogramma opgeroepen worden.

Eerst wordt de reguliere mammografie gedaan bij alle vrouwen. Met behulp van computersoftware wordt een geautomatiseerde nauwkeurige schatting (Volparamethode) van de densiteit van de borsten gedaan, nadat de vrouw voor screening geweest is.[10] De verkregen informatie wordt gekoppeld aan de screeningsuitslag. Als de densiteit 75% of meer is en de uitslag van de mammografie negatief (BI-RADS 1 of 2), komt de vrouw in aanmerking voor deelname aan het voorgestelde onderzoek. Deze vrouwen worden gerandomiseerd ingedeeld in twee groepen: een interventiegroep en een controlegroep. Alleen de interventiegroep krijgt een uitnodiging voor een aanvullende MRI. Van de controlegroep wordt alleen de gebruikelijk informatie uit het bevolkingsonderzoek geregistreerd, zoals de gegevens over intervaltumoren. Het onderzoek bestaat in totaal uit drie screeningsrondes van ieder twee jaar (in totaal zes jaar per deelneemster in de interventiegroep) en de totale looptijd van het onderzoek is tien jaar.

De directe medische kosten zullen in het kader van het proefbevolkingsonderzoek worden geregistreerd. Met behulp van een borstkankersimulatiemodel zal de incrementele kosteneffectiviteitsratio worden berekend van de interventie met MRI ten opzichte van het reguliere bevolkingsonderzoek.

Per MRI-onderzoekscentrum zou het ongeveer 400 extra MRI's per jaar betekenen. De MRI wordt gedaan binnen acht weken na deelname aan het bevolkingsonderzoek. Het MRI-protocol voor dit onderzoek zal worden gestandaardiseerd in de deelnemende centra. De centra hebben aangegeven hieraan te willen meewerken.

Hieronder wordt ingegaan op een aantal aspecten van het onderzoek: de steekproefomvang, het studiedesign, de inzet van laboranten, de inzet van radiologen en de te verwachten foutpositieven.

2.2.1 Steekproefomvang

De aanvrager verwacht dat het aantal intervaltumoren kan dalen van gemiddeld 4,4 per 1.000 screeningsonderzoeken naar 2,5 per 1.000 screeningsonderzoeken. Op basis hiervan is geschat dat met de gekozen proefopzet dit verschil met voldoende statistische significantie (95%) aantoonbaar is, wanneer 7.237 vrouwen (met een negatief mammogram en hoge borstdensiteit) worden uitgenodigd in de interventiegroep. Er is rekening gehouden met het feit dat niet alle vrouwen de uitnodiging zullen accepteren. De aanvrager verwacht dat tweederde van deze groep vrouwen zal meedoen, dat wil zeggen 4.776. Er wordt gerekend met een 1:4 verhouding tussen de interventie- en de controlegroep, dat wil zeggen 7.237 vrouwen in de interventiegroep en 28.948 (4*7247) vrouwen in de controle-

groep. Uiteindelijk wordt het statistisch onderscheidend vermogen (*power*) van deze studieopzet bij deze aantallen en de geschatte verschillen geschat op 80%.

Het percentage vrouwen met een borstdensiteit van 75% of meer betreft ongeveer 5% van het totaal aantal deelnemende vrouwen aan het bevolkingsonderzoek borstkanker. Dat komt neer op 90.000 vrouwen over een periode van twee jaar (één screeningsronde). De totale studiepopulatie (interventie 7.237 en controle 28.948) bestaat uit 36.185 vrouwen. Er is dus ruimte om meer vrouwen uit te nodigen als de deelname tegenvalt.

2.2.2 *Het studiedesign, keuze voor prerandomisatie*

Het onderzoek betreft een geprerandomiseerde trial, want randomisatie gaat vooraf aan het vragen van toestemming aan vrouwen in de interventiegroep. Verder worden vrouwen in de controlegroep niet op de hoogte gesteld van het onderzoek. In een studie van deze omvang met deze lange looptijd is het voorstelbaar dat vrouwen die in een gerandomiseerde studie met een klassieke opzet in de controlegroep terecht zouden komen na de toestemmingsprocedure zelf op zoek gaan naar aanvullende onderzoeksmethoden. Dat is onterecht zolang nog niet is aangetoond dat dit wetenschappelijk verantwoord is en kan leiden tot contaminatie en een mogelijk verlies aan geldigheid van de uitkomsten van de studie. Het doel van prerandomisatie is om dit te voorkomen.

Vrouwen in de controlegroep weten daarom niet dat hun (anonieme) gegevens worden gebruikt voor dit onderzoek. Zij krijgen exact dezelfde behandeling als gebruikelijk in het reguliere bevolkingsonderzoek borstkanker, waarin vooralsnog geen onderscheid wordt gemaakt op basis van borstdensiteit. De gegevens die van deze vrouwen nodig zijn (optreden van eventuele intervalcarcinomen) kunnen achterhaald en gebruikt worden voor de studie door koppeling van de screeningsgegevens aan de cijfers van de Nederlandse Kankerregistratie en het CBS. Dit gebeurt nu ook al routinematig.

2.2.3 *De radiologisch laboranten*

De radiologisch laboranten, ‘in de bus’, voeren alleen de routinematige borstkankerscreening met digitale mammografie uit. Zij hebben geen enkele bemoeienis met het onderzoek, aangezien de densiteit automatisch met computersoftware wordt bepaald. Pas achteraf worden de vrouwen in de interventiegroep hierover via de post geïnformeerd.

2.2.4 *De inzet van de radiologen, beoordeling MRI*

De radiologen beoordelen de MRI-beelden volgens vooraf afgesproken en *state of the art* richtlijnen. De afspraken worden vastgelegd in een werkdocument dat aan alle betrokken centra wordt uitgedeeld. De protocollen ter beoordeling van de MRI worden opgesteld in overleg met een andere onderzoeksgroep (van het Erasmus MC) die een soortgelijke studie doet naar het gebruik van MRI bij familiair verhoogd risico op borstkanker. Per MRI moeten twee onafhankelijke radiologen de MRI beoordelen en tot consensus komen over het te volgen beleid. De radiologen krijgen een training om de uitvoering en de beoordeling van MRI's te standaardiseren.

2.2.5 *Foutpositieven*

Toezicht op het aantal foutpositieven vindt voortdurend plaats, ook binnen het reguliere bevolkingsonderzoek. Gedurende de studie worden alle MRI-uitslagen die een indicatie zijn voor medisch handelen (BI-RADS uitslag 3,4 of 5) nogmaals centraal beoordeeld door een expertpanel, waarmee de deelnemende radiologen feedback krijgen op hun verwijsgedrag. Bovendien wordt al in het begin van de studie, na de eerste 750 MRI's, gekeken naar het aantal onterechte verwijzingen en het aantal onterechte biopsieën. Ligt het aantal onterechte verwijzingen boven de 25% of het aantal onterechte biopsieën boven de 15%, dan wordt overlegd of modificatie van de interventie (verwijscriteria) noodzakelijk is en kan stopzetting van de studie overwogen worden. Te verwachten valt dat het percentage foutpositieven in vervolgrondes lager is dan in de eerste ronde. Uit de literatuur blijkt dat het beschikbaar hebben van een voorgaande MRI de kans op een onterechte verwijzing voor nader onderzoek verlaagt.[11]

2.2.6 *Kwaliteit van leven*

De studie tracht meer inzicht te verkrijgen in de beleving van de vrouwen en de invloed die het ondergaan van aanvullende MRI heeft op de kwaliteit van leven. Daartoe maakt de aanvrager gebruik van een paar zogenoemde generieke vragenlijsten en een specifieke vragenlijst. Daarin zullen onder andere de effecten van foutpositieve en foutnegatieve uitslagen betrokken worden.

2.3 Werven en informeren van deelneemsters aan het onderzoek

De deelneemsters worden geworven onder vrouwen die deelnemen aan het reguliere bevolkingsonderzoek naar borstkanker. Deelneemsters worden alleen geworven in die regio's die gelegen zijn in de bedieningsgebieden van ziekenhuizen waar de MRI's kunnen worden uitgevoerd. Vrouwen in de leeftijd 50-75 jaar krijgen volgens de gangbare procedure een oproep om deel te nemen aan het bevolkingsonderzoek borstkanker.

Alleen vrouwen met een negatief mammogram en hoge borstdensiteit en die vervolgens worden ingeloot in de beoogde interventiegroep, worden per post benaderd. Zij krijgen uitleg over het onderzoek en het verzoek om in te loggen op speciaal voor het onderzoek in het leven geroepen website. De informatie (post en website) omvat alle aspecten van het meedoen aan bevolkingsonderzoek in het algemeen en dit onderzoek in het bijzonder. Onderdeel van het informatiepakket is de brochure 'medisch wetenschappelijk onderzoek', waarin duidelijk staat dat vrouwen zonder opgaaf van reden deelname aan het onderzoek mogen weigeren. De aanvrager wil echter ook graag iets kunnen zeggen over de redenen waarom vrouwen besluiten niet deel te nemen. Daarom wordt vrouwen die niet willen deelnemen gevraagd op de website aan te geven waarom zij niet mee willen doen. Ook hiervan wordt duidelijk gemaakt dat dit geheel vrijwillig is en dat het al dan niet gevolg geven aan dit verzoek geen consequenties heeft voor verdere deelname aan de routinematige screening.

Vrouwen geven via de website aan of zij geïnteresseerd zijn. Als dit het geval is, worden zij telefonisch benaderd. Dan kunnen ze nog nadere informatie krijgen en hun vragen worden beantwoord. Vervolgens beslissen ze of ze inderdaad mee willen doen. Vrouwen die meer bedenktijd nodig hebben, kunnen later worden teruggebeld. Besluit de vrouw tot deelname, dan wordt tijdens het gesprek een afspraak voor MRI gemaakt. Deze wordt schriftelijk bevestigd. Bij het bezoek aan het MRI-centrum tekent de vrouw een toestemmingsverklaring.

In de informatie is verder beschreven dat deelneemsters die nog nadere medische vragen hebben over het onderzoek deze kunnen stellen aan een betrokken arts-onderzoeker of aan een onafhankelijk arts. In alle gevallen wordt de vrouw erop gewezen dat deelname aan het onderzoek vrijwillig is en dat zij op ieder willekeurig moment kan besluiten om deelname stop te zetten. Persoonsgegevens worden gecodeerd en zijn alleen voor de onderzoekers en bevoegde personen toegankelijk. Daarnaast is informatie opgenomen over de vergoeding, verzekering, aansprakelijkheid en klachtenprocedure.

2.4 Tijdsplanning

De studie zal relatief lang duren, in totaal tien jaar, omdat er meerdere screeningsrondes nodig zijn. De belangrijkste uitkomst van deze studie waarop de aanvrager effect verwacht is het aantal intervalcarcinomen, daarom is er per definitie een verschil nodig tussen een eerste en tweede ronde screening. Toevoeging van MRI aan het onderzoek zal waarschijnlijk leiden tot verhoogde sensitiviteit in vergelijking met mammografie alleen. In een eerste screeningsronde met een sensitievere methode is het gevonden aantal positieven echter hoger, omdat er bij een eerste ronde een groter aandeel makkelijk te detecteren tumoren aanwezig zal zijn.[12] Dat wil echter niet per definitie zeggen dat de programmasensitiviteit van opeenvolgende rondes ook hoger zal zijn. Omdat het interval tussen ronde een en twee alleen daarom geen goed beeld kan geven, heeft de aanvrager nog een derde ronde toegevoegd voor het interval tussen ronde twee en drie. Naar verwachting zal na de derde ronde het verschil tussen de twee strategieën (mammogram alleen of mammogram en MRI) gestabiliseerd zijn.

De looptijd kan niet worden verkort, bijvoorbeeld door samenwerking met buitenlandse onderzoeksgroepen of door het gebruik van data uit het verleden. Er zijn geen studies in het buitenland gaande met een dergelijke opzet. Het is ook niet mogelijk, ondanks de digitalisering van de mammografie, om retrospectief röntgenmammogrammen te beoordelen op densiteit. De ruwe data die nodig zijn om de densiteit van het borstweefsel te bepalen kosten erg veel computergeheugen en worden daarom niet standaard opgeslagen. De opgeslagen data zijn van onvoldoende kwaliteit voor densiteitsbepalingen. Het is dus niet mogelijk om via mammogrammen uit het verleden deelneemsters met hoge densiteit achteraf alsnog op te roepen.

2.5 Financiering

Het onderzoek kent verschillende financieringsbronnen: eigen geld van het Julius Centrum, ZonMW (samen met het onderzoek van het Erasmus MC), Pink Ribbon, KWF en Bayer/Schering. Financiering vanuit de industrie was mogelijk omdat deze firma de contrastvloeistof voor MRI levert. Contractueel is vastgelegd dat deze firma geen enkele zeggenschap heeft over de opzet en de uitvoer van de studie en ook niet over de evaluatie en de publicatie van de onderzoeksresultaten.

Hoofdstuk **3**

Toetsing vergunningaanvraag

3.1 Wetenschappelijke deugdelijkheid

3.1.1 Keuze voor MRI

De aanvrager kiest voor aanvullende MRI om vrouwen met hoge borstdensiteit te onderzoeken. Een andere mogelijkheid zou echografie zijn. Beide technieken hebben niet het nadeel van het maskerend effect van mammografie bij borstweefsel met een hogere densiteit. Aan beide technieken kleven voor- en nadelen. Voor echografie is het hoge aantal foutpositieve uitslagen een negatief aspect. Daarnaast is de reproduceerbaarheid laag en kunnen de schijnbaar lage kosten ten opzichte van MRI toch hoger uitvallen dan verwacht, omdat het nauwkeurig maken van een echo zeer goed geschoold personeel (radioloog) vereist, en de handeling lang duurt. Relatief nieuw is de driedimensionale (3D-)echografie. Hierover zijn nog geen gegevens beschikbaar om validiteit, gevoeligheid en kosten te kunnen vergelijken met MRI. De uitvoering van een MRI als aanvulling op de reguliere mammografie geeft weliswaar ook een kans op foutpositieve uitslagen, maar leidde bij vrouwen met BRCA 1/2-mutaties tot aanzienlijk hogere sensitiviteit dan ofwel mammografie ofwel MRI alleen.[13] De keuze van de aanvrager voor MRI vindt de commissie dan ook gerechtvaardigd.

3.1.2 *Deugdelijkheid steekproefomvang*

De aanvrager heeft de verwachte uitkomst van het onderzoek (minder intervaltumoren met aanvullende MRI bij vrouwen met hoge densiteit) kwantificeerbaar en toetsbaar gemaakt met behulp van gegevens uit de literatuur en het Nederlands bevolkingsonderzoek. Zo onderbouwt de aanvrager de berekening dat het aantal intervaltumoren in de interventiegroep zou moeten dalen van 4,4 naar 2,5 per duizend vrouwen. In die berekening is het deel van de vrouwen in de interventiegroep dat niet wenst mee te doen (geschat op een derde deel) verdisconteerd.

Om zo min mogelijk MRI's te hoeven doen (in het bijzonder vanwege de beperkte MRI-capaciteit en de kosten daarvan), past de aanvrager de randomisatie toe met een verhouding van 1:4. Dat wil zeggen dat er vier keer zoveel vrouwen in de controlegroep komen als in de interventiegroep. De commissie constateert dat een nog schevere verhouding niet zal leiden tot nog minder vrouwen in de interventiegroep.

Op basis hiervan berekent de aanvrager (zie Steekproefomvang) dat er 7.237 vrouwen uitgenodigd moeten worden in de interventiegroep. Volgens de 1:4 verhouding bestaat dan de controlegroep uit 28.948 (4*7247) vrouwen.

De commissie is van mening dat de aannames deugdelijk zijn. De commissie vindt het goed dat de scheve randomisatieverhouding ertoe leidt dat zoveel mogelijk vrouwen een vooralsnog niet bewezen effectief invasief onderzoek wordt bespaard (zie ook Nut en risico's van deelname aan het onderzoek). De berekeningen van de aanvrager leiden volgens de commissie tot een steekproef met een voldoende omvang en power om de hypothese na afloop van de studie te kunnen aantonen of te weerleggen.

3.1.3 *Beperken van foutpositieve uitslagen*

Het schatten van het aantal foutpositieven is moeilijk, en tevens onderwerp van het onderzoek. Er wordt uitgegaan van een studie van Berg waarin het aantal foutpositieven 17% bedraagt en benigne biopten 9%.[14] De aanvrager tracht op verschillende manieren het aantal foutpositieven en mogelijk onnodige ingrepen zo laag mogelijk te houden (herhaalde centrale beoordeling, vervolg MRI-onderzoek en echografie voor biopsie na positieve MRI, tussentijdse evaluatie van de resultaten). Ook de keuze voor MRI als aanvullende diagnostiek naast röntgenmammografie boven echografie draagt bij aan een minder groot aantal foutpositieven. Het is onmogelijk om alle foutpositieven uit te sluiten. Zonder het effect

van MRI op het aantal intervaltumoren te kennen, kan niet goed worden vastgesteld wat een acceptabel aantal foutpositieven is, omdat dit afhankelijk is van de verhouding tussen terecht- en foutpositieven. De commissie is van mening dat de onderzoekers voldoende hebben aangetoond dat zij het aantal foutpositieven in de studie zo gering mogelijk proberen te houden.

3.1.4 Kwaliteit van leven

De studie heeft ook aandacht voor de kwaliteit van leven van de deelnemende vrouwen en in het bijzonder de foutpositieven en foutnegatieven. Daartoe maakt de aanvrager gebruik van een drietal verschillende kwaliteit van leven vragenlijsten. Die vragenlijsten dienen elk een verschillend doel. De generieke vragenlijsten (EORTC, EQ5D) hebben als voordeel dat de resultaten kunnen worden vergeleken met andere groepen mensen met andere gezondheidsrisico's (generaliseerbaarheid). Daarnaast kunnen de utiliteiten van de EQ5D gebruikt worden om de standaard kosteneffectiviteitanalyse uit te breiden met een kostenutiliteitsanalyse, waarbij de gezondheidseffecten worden uitgedrukt in voor kwaliteit gecorrigeerde levensjaren ('Quality Adjusted Life Years', QALY's). De meer specifieke vragenlijsten (COS-BC-1 en 2) zijn weer van belang om meer inzicht te krijgen in de mogelijk specifieke problemen van de gescreende vrouwen. Vaak zijn dergelijke vragenlijsten, afhankelijk van hun opbouw, ook meer in staat om veranderingen in de gezondheidstoestand en kwaliteit van leven aan het licht te brengen, wanneer ze herhaald (bij elke screeningsronde bijvoorbeeld) worden afgenomen.

De commissie vindt dat de aanvrager voldoende aandacht heeft voor de kwaliteit van leven van de deelnemende vrouwen en vindt het ook goed dat hierbij in het bijzonder ook aandacht wordt besteed aan mogelijke verschillen als gevolg van foutpositieve en foutnegatieve uitslagen.

3.2 Overeenstemming met de wettelijke regels voor medisch handelen

Het vereiste dat in deze paragraaf aan de orde komt (artikel 7, eerste lid) heeft betrekking op regels die in diverse wetten te vinden zijn. De commissie concentreert zich op het Besluit bevolkingsonderzoek, dat eveneens van toepassing is op het beoogde project. Het besluit stelt concrete eisen ter bescherming van proefpersonen: de schriftelijke informatie moet onder meer betrekking hebben op het doel, de aard en de duur van het onderzoek. Deze informatie moet zo verstrekt worden dat deze redelijkerwijs te begrijpen is voor de betrokkene. Verder moeten

deelnemers bedenktijd kunnen krijgen om weloverwogen toestemming te kunnen geven.

Zonder schriftelijke toestemming is deelname aan wetenschappelijk onderzoek verboden. De informatie over het onderzoek aan de deelnemers geeft de commissie geen aanleiding tot opmerkingen. De commissie is van mening dat de vrouwen voldoende ingelicht worden om een weloverwogen keuze te kunnen maken over deelname aan de studie. Daarnaast krijgen ze voldoende bedenktijd om te overwegen of ze wel of niet mee zullen doen aan het onderzoek en is duidelijk dat ze zich altijd zonder opgave van reden kunnen terugtrekken en dat dit geen invloed heeft op hun deelname aan het reguliere bevolkingsonderzoek.

Het aangevraagde onderzoek betreft echter een geprerandomiseerd onderzoek, waarbij de controlegroep niet om toestemming gevraagd wordt. Om toch aan de bescherming van proefpersonen te voldoen gelden extra toetsingscriteria waaraan dergelijk onderzoek moet voldoen.[15] Deze bespreekt de commissie hieronder.

3.2.1 Prerandomisatie

Prerandomisatie wil zeggen dat de beoogde deelneemsters eerst worden ingedeeld in de interventie- en controlegroep, voordat zij worden uitgenodigd om deel te nemen en om toestemming worden gevraagd. Ethisch kan het als correcter worden gezien om eerst toestemming te vragen voorafgaand aan de loting, omdat ook de loting als deel van het onderzoek kan worden gezien.

Er zijn twee zwaarwegende redenen waarom de aanvrager kiest voor prerandomisatie. Ten eerste is er de vrees dat bij een klassieke gerandomiseerde opzet gedurende de looptijd van het onderzoek zogenoemde contaminatie ontstaat. Wanneer randomisatie pas plaatsvindt na toestemming en dus ook na voorlichting over het risico van hoge borstdensiteit, is de kans reeël dat vrouwen met hoge borstdensiteit die in de controlegroep terechtkomen uit eigen beweging vervolgonderzoek aanvragen. Als dergelijke contaminatie van de controlegroep frequent zou gebeuren, komt de interne validiteit van het onderzoek in gevaar. Daardoor zal het moeilijker zo niet onmogelijk worden om het effect van aanvullende MRI nog wetenschappelijk aan te kunnen tonen of te weerleggen. Overigens bestaat er ook een kans dat contaminatie optreedt door algemene bekendheid over de risico's van hoge borstdensiteit, bijvoorbeeld via de media.

Een tweede overweging van de aanvrager om tot prerandomisatie over te gaan, is dat op dit moment aan vrouwen in de controlegroep niets extra's geboden kan worden. Anders dan mammografie zijn er geen bewezen effectieve methoden om de detectie van borstkanker te verhogen. Ook zijn er geen metho-

den om de densiteit van het borstweefsel of de effecten daarvan te verminderen. Dit zou in een studie zonder de voorgestelde opzet met prerandomisatie tot veel onnodige onrust kunnen leiden in de controlegroep.

Om een geprerandomiseerde studie uit te mogen voeren, moet de studieopzet voldoen aan drie toetsingscriteria. De opzet:

1 moet leiden tot nieuwe inzichten (dat is het belang van het onderzoek)
2 moet voldoen aan het criterium van subsidiariteit
3 moet voldoen aan het criterium van proportionaliteit.

Wat betreft het eerste criterium zal met de gekozen uitkomstmaten en de grootte van de studie voldoende bewijskracht geleverd worden voor de werkzaamheid van het toevoegen van MRI aan de borstkankerscreening bij vrouwen met hoge borstdensiteit. De studie zal bijdragen aan verbetering van de borstkankerscreening en mogelijk de sterfte aan borstkanker reduceren. Ook een negatieve uitkomst is waardevol: in dat geval levert de studie een goede wetenschappelijke onderbouwing om MRI niet toe te voegen aan het reguliere bevolkingsonderzoek borstkanker, wanneer uit oogpunt van gepersonaliseerde screening daarnaar vraag ontstaat.

Het tweede criterium impliceert dat een geprerandomiseerde studie alleen gerechtvaardigd is wanneer er geen alternatieve onderzoeksopzet mogelijk is. Zoals hierboven betoogd is dat het geval, want een klassieke gerandomiseerde studieopzet leidt potentieel tot ernstige contaminatie, wat de validiteit van het onderzoek aantast.

Het derde criterium houdt in dat de belasting voor de deelnemers gering moet zijn en de nadelen van het deelnemen aan het onderzoek klein. Ook hieraan wordt naar de mening van de commissie voldaan, waarschijnlijk zelfs beter dan in een klassieke gerandomiseerde onderzoeksopzet. In een klassieke opzet zouden vrouwen in de controlegroep al geïnformeerd zijn over de risico's van hoge borstdensiteit, zonder dat er een bewezen alternatief beschikbaar is voor verbeterde diagnostiek of risicovermindering. Dit zou onnodig tot veel onrust kunnen leiden. In de huidige opzet zijn de vrouwen onwetend over hun status (zowel over het feit dat zij een relatief hoge borstdensiteit hebben, als over het feit dat zij anoniem in de controlegroep zijn ingedeeld), maar zij worden hierdoor niet achtergesteld: zij ontvangen niet meer of minder zorg dan iedere andere vrouw in dezelfde leeftijdsgroep die aan het reguliere bevolkingsonderzoek deelneemt.

Omdat de vrouwen in de controlegroep er geen nadeel van ondervinden dat zij niet op de hoogte zijn van het onderzoek en omdat het voor de evaluatie van het onderzoek vrijwel zeker essentieel is, oordeelt de commissie dat in dit specifieke onderzoek prerandomisatie acceptabel is.

Voor de vrouwen die zijn ingeloot in de interventiegroep geldt dat zij uitgebreid worden voorgelicht over de studie en de nut-risicoverhoudingen. Zij krijgen naast de mededeling dat ze in een hoogrisicogroep vallen ook een aanvullende methode van diagnostiek geboden, de MRI. Hoewel het nut van die aanvullende methode het onderwerp is van de studie, meent de commissie dat het toch aannemelijk is dat de vrouwen niet onnodig belast worden doordat zij pas na randomisatie worden ingelicht over de studie.

3.3 Nut en risico's van deelname aan het onderzoek

De deelnemende vrouwen in de interventiegroep kunnen direct profijt hebben van deelname aan de studie, wanneer een bij het mammogram gemiste tumor wel aan het licht komt bij de aanvullende MRI.

Voor de vrouw kan het ondergaan van een MRI mogelijk nadelig zijn, bijvoorbeeld als tijdens het onderzoek claustrofobie optreedt, als overgevoeligheid blijkt voor de contrastvloeistof, doordat het onderzoek mogelijk ongerustheid meebrengt en vanwege de tijdsinvestering die het de deelneemster kost.

Het grootste nadeel van de MRI voor de individuele vrouw ontstaat wanneer het MRI-onderzoek leidt tot een foutpositieve uitslag van de MRI, zeker wanneer dat tot (achteraf bezien) onnodige invasieve ingrepen leidt. De aanvrager onderkent dit zwaarwegende en belastende nadeel en neemt maatregelen om het aantal foutpositieven te monitoren en desnoods de studie stop te zetten als dit aantal te groot blijkt te zijn. Zoals in Kwaliteit van leven is beschreven wordt ook bestudeerd of dit invloed heeft op de kwaliteit van leven van de deelnemende vrouwen.

Voor de vrouwen in de controlegroep is er geen nadeel. Zij weten niet van het onderzoek en voor hen is het bevolkingsonderzoek naar borstkanker exact gelijk aan het nu gebruikelijke bevolkingsonderzoek. Er wordt hun geen gevalideerde en bewezen nuttige aanvullende methode van screening onthouden, er worden hun geen extra handelingen opgelegd en er is geen aanleiding voor gedragswijzigingen door het onderzoek.

3.4 Het belang voor de volksgezondheid

In hoofdstuk 1 stelde de commissie vast dat het in de aanvraag beschreven onderzoek een combinatie is van wetenschappelijk onderzoek en bevolkingsonderzoek. Daarvoor geldt dat vergunning kan worden geweigerd als het 'het belang van de volksgezondheid een dergelijk onderzoek niet vordert'. Van deze omstandigheid is naar het oordeel van de commissie geen sprake. Het project is gericht

op een serieus volksgezondheidsprobleem en het is van algemeen nut als er door deze studie mogelijk een goed bruikbare methode bijkomt om vrouwen in een risicogroep op borstkanker te screenen. Ook als de uitkomst negatief is, is dit onderzoek van algemeen belang: dan weten we tenminste dat aanvullende MRI geen toegevoegde waarde heeft.

Hoewel het hogere risico op borstkanker door hoge densiteit al langer bekend is, is pas de laatste jaren de aandacht in de lekenpers toegenomen, vooral in de Verenigde Staten. Dit leidt tot verhoogde bekendheid van vrouwen met het onderwerp en onrust over de densiteit van hun borsten en de daaraan gelieerde risico's. Inmiddels zijn ook in Nederland in de Tweede Kamer vragen gesteld over het onderwerp. Zodra vrouwen hierdoor in grote aantallen om aanvullende diagnostiek gaan vragen, bestaat de kans dat technieken zoals echografie en MRI toegepast gaan worden zonder dat hier deugdelijke wetenschappelijke gronden voor zijn. In een dergelijke situatie is het veel moeilijker, zo niet onmogelijk, om nog een gedegen wetenschappelijk onderzoek te doen naar het vermeende nut van een aanvullende interventie met MRI voor deze vrouwen. Het is volgens de commissie daarom in het belang van de volkgezondheid om dit onderzoek nu te doen en niet uit te stellen.

Hoofdstuk **4**

Conclusie

In dit advies heeft de Commissie WBO een vergunningaanvraag beoordeeld van het Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde te Utrecht. Het betreft een wetenschappelijk onderzoek naar het nut van aanvullende MRI naast de reguliere mammografie in het bevolkingsonderzoek naar borstkanker voor vrouwen met hoge borstdensiteit.

De commissie stelt vast dat het in de aanvraag beschreven onderzoeksvoorstel een combinatie betreft van vergunningplichtig bevolkingsonderzoek en wetenschappelijk onderzoek (‘toetsing vergunningplicht’). Het voorstel voldoet aan het vereiste van ‘wetenschappelijke deugdelijkheid’ (3.1): de opzet is goed en de mogelijke meerwaarde van aanvullende MRI en het aantal benodigde deelneemsters om de onderzoeksvragen te beantwoorden is voldoende onderbouwd. Zij vindt ook dat is voldaan aan het vereiste van ‘overeenstemming met wettelijke regels voor medisch handelen’ (3.2), de vrouwen in de interventiegroep worden goed geïnformeerd over het onderzoek en eventuele nadelen en krijgen voldoende tijd om te bedenken of zij al dan niet zullen deelnemen. In dit onderzoek is gekozen voor prerandomisatie waarvoor additionele toetsingscriteria gelden. In dit specifieke geval voldoet prerandomisatie volgens de commissie aan deze criteria. De vrouwen in de controlegroep ondervinden geen enkel nadeel van het feit dat zij niet op de hoogte worden gesteld van het feit dat zij onderdeel uitmaken van de controlegroep. Zij ondergaan geen extra handelingen, het onderzoek geeft geen aanleiding tot gedragswijziging en er wordt hen tegelijkertijd ook geen bewezen effectief aanvullend onderzoek onthouden. Zij doen immers

gewoon mee met het reguliere bevolkingsonderzoek zoals dat nu is. De aanvullende MRI heeft mogelijk direct nut voor de deelneemsters, maar er kunnen ook risico's aan zijn verbonden (3.3). Het voornaamste risico is de kans op een foutpositieve uitslag met de gevolgen van onnodig extra onderzoek en/of behandeling en de (tijdelijke) onrust dat dit teweeg kan brengen. De aanvrager houdt volgens de commissie voldoende rekening met dit risico en zal het onderzoek eventueel stoppen als het aantal foutpositieven onverhoopt onevenredig hoog is.

Ook aan de vereiste in de WBO dat het niet 'het belang van de volksgezondheid niet vordert' (3.4), dat van belang is als er tevens sprake is wetenschappelijk onderzoek, is volgens de commissie met dit onderzoek voldaan en dit weegt op tegen de individuele risico's van de vrouw. De commissie stelt in deze context ook vast dat het algemene bewustzijn van het probleem van hoge borstdensiteit snel toeneemt, met als mogelijk gevolg dat allerlei belanghebbenden, niet in de laatste plaats de vrouwen zelf, kunnen aandringen op dergelijk aanvullend onderzoek. Daarom vindt de commissie het van belang dit onderzoek niet uit te stellen.

De commissie concludeert dat het wetenschappelijk onderzoek in deze aanvraag voldoet aan de wettelijke criteria van de WBO. Op basis van deze toetsing adviseert de commissie de minister de gevraagde vergunning te verlenen voor de duur van het onderzoek, rekening houdend met mogelijke uitloop.

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A De adviesaanvraag

B De commissie

Bijlagen

Bijlage **A**

De adviesaanvraag

Op 27 december 2010 ontving de voorzitter van de Gezondheidsraad van de minister van Volksgezondheid Welzijn en Sport de onderstaande adviesaanvraag over WBO-aanvraag voor onderzoek naar borstkankerscreening met MRI bij vrouwen van 50-75 jaar met hoge mammografische densiteit binnen het bevolkingsonderzoek naar borstkanker:

Op 1 december 2010 ontving ik een aanvraag namens het Julius Centrum te Utrecht in het kader van de Wet op het bevolkIngsonderzoek voor een vergunning voor het bevolkingsonderzoek naar borstkanker. Het betreft een onderzoek naar borstkankerscreening met MRI bij vrouwen van 50-75 jaar met hoge mammografische densiteit binnen het bevolkingsonderzoek naar borstkanker.

Ik ben van oordeel dat er sprake is van een vergunningplichtig bevolkingsonderzoek en acht de aanvraag voldoende gedocumenteerd. Ik leg u de aanvraag hierbij daarom voor ter toetsing aan de wettelijke criteria.
Gehoord uw beoordeling besluit ik over vergunningverlening.

Hoogachtend,
de Minister van Volksgezondheid,
Welzijn en Sport, namens deze,
de waarnemend directeur
Publieke Gezondheid,
drs. C.L. Goebel

Bijlage **B**

De commissie

- prof. dr. J.J.M. van Delden, *voorzitter*
  hoogleraar medische ethiek, Universitair Medisch Centrum Utrecht
- drs. R.J. Boumans, *waarnemer*
  Inspectie voor de Gezondheidszorg, Amsterdam
- prof. mr. dr. J.C.J. Dute
  gezondheidsjurist, Universiteit van Amsterdam
- prof. dr. J. Gussekloo
  hoogleraar huisartsgeneeskunde, Leids Universitair Medisch Centrum
- prof. dr. L.P. ten Kate
  emeritus hoogleraar klinische genetica, VU medisch centrum, Amsterdam
- prof. dr. M.H. Prins
  hoogleraar klinische epidemiologie, Maastricht Universitair Medisch Centrum
- dr. E.M.A. Smets
  psycholoog, Academisch Medisch Centrum, Amsterdam
- prof. dr. F. Sturmans
  emeritus hoogleraar epidemiologie, Geertruidenberg
- dr. M.F.M. Langelaar, *secretaris*
  Gezondheidsraad, Den Haag
- dr. L.G.M. van Rossum, *secretaris*
  Gezondheidsraad, Den Haag

University Medical Center
Utrecht

Date 21 August 2024

Regarding Horizon Odelia

Dear Sir,

On behalf of Dr. W.B. Veldhuis we would like to assure that the privacy of the patients included in the research carried out has been handled in conformance with the law and regulations of The Netherlands regarding patient data.

According to the Dutch law and regulations, anonymous data is not covered by AVG/GDPR. This study does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). and thus ethical consent/review is not applicable. The use of completely anonymous, non-reducible, non-pseudonymized, for the HORIZON ODELIA study therefore falls within the laws and regulations."

Sincerely,

Prof dr. J. Hendrikse
Medical Scientific Manager

ValidSigned door J. Hendrikse
op 21-08-2024

Drs. L.A.A. van Reeuwijk
Division manager

ValidSigned door L.A.A van Reeuwijk-Bukkems
op 21-08-2024

UMC Utrecht, locatie AZU

Bezoekadres:
Heidelberglaan 100
3584 CX Utrecht

Postadres:
Huispostnummer F03.821
Postbus 85500
3508 GA Utrecht

www.umcutrecht.nl

Participant Recruitment and Data Management in the ODELIA project for VHIO

Participant Recruitment

Participants for this study on breast cancer detection using MRI imaging will be retrospectively identified from existing clinical and imaging datasets at The Clinic University Hospital. These datasets include individuals who underwent breast MRI scans for diagnostic or screening purposes between 2005 and 2023. Patients who underwent bilateral mastectomies before the scan will be excluded from the study.

Recruitment will be based solely on pre-existing records; no active patient enrollment or additional imaging will be required. All data used will comply with institutional and ethical guidelines for secondary data usage, ensuring that only necessary and de-identified information is accessed for the study.

Data Collection and Storage

Breast MRI scans and clinical data will be collected at The Clinic University Hospital in Barcelona and stored on the VHIO server. The collection and processing of image data from study participants will be limited to the data necessary to achieve the study's objectives.

The extracted data will include imaging in the Digital Imaging and Communications in Medicine (DICOM) format and essential clinical parameters, such as patient demographics, medical history, and breast cancer diagnosis outcomes.

All personal identifiers will be removed during data processing. A secure alphanumeric code will replace identifying information to ensure participant anonymity. The linkage between these codes and patient identities will remain encrypted and stored only at the originating clinical center, accessible exclusively by the local investigator.

The ODELIA research group at VHIO will take all necessary precautions to ensure data confidentiality and compliance with European and National data protection regulations, as well as ICH-GCP standards. Technical and organizational measures will be in place to protect personal data from unauthorized access, disclosure, accidental loss, or alteration. The research team at the Clinic University Hospital will maintain the confidentiality of subjects by assigning them alphanumeric codes. The link between these codes and actual personal data will be securely stored at the clinical center, with access restricted to the local investigator. Source data will be retained for 5 years after publication in a peer-reviewed journal and will be

available for inspection by authorized personnel, including the Chief/Principal Investigators, Study Coordinator, and Statistician. Source documents will be accessible for monitoring and audit purposes by the Ethics and Research and Development departments and regulatory bodies upon request.

Data Format

Digital medical imaging, specifically breast MRI scans, will be collected. To ensure efficient analysis workflow and compatibility across different scanners, the original DICOM format (standard for hospital imaging data storage) will be converted to the NIfTI data format. Radiological images will undergo a quality check to ensure completeness and data integrity, with any necessary repairs carried out as needed.

Clinical demographics and outcomes will be collected with a focus on patient privacy. Only essential clinical information will be used, collected in HTML format within the REDCap Platform on the Radiomics Group's server at VHIO.

Ethical Considerations

The study design prioritizes patient confidentiality and adheres to ethical standards for data handling and secondary usage. All procedures for data collection, storage, and processing have been reviewed and approved by institutional ethics boards. Participants' anonymity will be rigorously maintained, and their data will be used solely for the stated research purposes.

Evaluation of machine learning techniques for the detection of breast cancer in radiological data

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [9].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A
Project Leader:	Prof. Dr. med. Dr. sc. hum. Dipl.-Phys., MBA Andreas Boss Rämistr. 100 8091 Zürich Tel. 044-2553677 Email: andreas.boss@usz.ch

Study Title	*Evaluation of machine learning techniques for the detection of breast cancer in radiological data*

The project leader (main centre) and the investigator (at KSA) have approved the protocol version ***1.0 (dated 15.03.2021),*** and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Project leader (USZ)

Site *University Hospital Zurich*

Name:

Date: _____ Signature: _____

Sponsor: identical to project leader

Name:

Date: _____ Signature: _____

Local Project Leader at local center (KSA):

Site *Kantonsspital Aarau*

Name of Local Project Leader: _____

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*

1 BACKGROUND AND PROJECT RATIONALE

1.1 Background Breast Imaging

Breast cancer is the most frequent cancer in women with an incidence of 12.3% in the normal population [1]. The disease of breast cancer is the second most common cause of death by cancer [2]. In Europe, every year 216'000 cases of breast cancer are newly diagnosed, and more than 79'000 deaths per year are registered.

Apart from genetic disposition, hormonal influences such as estrogen replacement therapy and oral contraception are discussed as potential risk factors. In the meantime, more than 19 million women have been included in the mammography screening program of Great Britain, and more than 117'000 breast cancers have been detected [3]. The International Agency for Research in Cancer (IARC) of the World Health Organisation, com-prised of 24 experts from 11 countries, deduced from all available data of breast cancer screenings that a 35% reduction of mortality can be observed in countries providing a common mammography screening program to women in the age between 50-69 years. The cantons of the western part of Switzerland, which implemented a screening program already in the early 90s, report a similar reduction in the order by 35%, whereas the cantons of German speaking Switzerland without a dedicated screening program observed a reduction by only 14% [4].

In spite of the successes of the organized screening programs, screening mammography has been the subject of strong criticism within the last two years. The Swiss Medical Board (SMB), an expert council sustained by the Swiss Medical Association (FMH), the Swiss Academy of Medical Science (SAMW), and the Gesundheitsdirektorenkonferenz GDK, recommends against a systematic screening program in Switzerland. The authors of the respective report point out that in 1.000 patients undergoing mammography screening, 100 women suffer from false-positive findings requiring further investigations or unnecessary treatments (NZZ am Sonntag, 2. Februar 2014, "Mammografie-Screening nutzt Frauen zu wenig") [5]. In the opinion of the SMB, screening programs exhibit an unfavorable cost-benefit relationship. They calculate that for each safed life year with good life quality ("QALY") an amount of CHF 248.000 needs to be spend by the society, which the SMB believes is too high regarding the absolute reduction in mortality of 1 in 1.000 patients included in a breast cancer screening program.

Moreover, the false-positive findings are a substantial concern of the SMB. The risk of obtaining a false-positive report after mammography is in the order of 4% according to the SMB, frequently resulting in subsequent biopsy or even operation. This may be due to the fact that Swiss radiologists in general not even read 500 mammographies per year with European guidelines recommending at least 5.000 mammographies per year. These low numbers of mammographies per radiologist in Switzerland may result in both, lower sensitivity for the detection of breast cancer compared to European standards leaving the patient in false security, and high number of false positive findings. However, even in highly standardized screening programs a positive predictive value (PPV) of conventional mammography in the range between 30-45% is reported depending on the respective screening program [6]. This means that more than half of the women with suspicious findings in conventional mammography undergo further imaging examinations or biopsies without relevant breast disease. These examinations result in unnecessary pain, additional costs, and psychological stress in these patients.

1.2 Computer-aided diagnosis in mammography

The first computer-aided detection/diagnosis (CAD) systems have been developed more than 20 years ago [7]. In general CAD systems are classified in two categories: computer-aided detection (CADe) and computer-aided diagnosis (CADx) systems. CADe systems are intended to help the radiologist in detecting and locating abnormal areas in mammographies, whereas CADx systems are developed to diagnose and classify benign and malignant lesions [8]. Several machine learning techniques for breast lesion detection and localization have been evaluated including K-nearest neighbor (KNN), support vector machine (SVM), and artificial neural networks (ANN). So

far no commercial technique or system has reached significant acceptance within the radiological community.

2.1.3 Machine learning

Most of the machine learning techniques exist since several decades, however they were hardly applied in imaging tasks due to the lack of sufficient computational power required for optimization ("training") of sophisticated techniques such as deep neuronal networks and the lack of structured databases, which could be used for supervised learning.

This situation changed significantly within recent years. The development of sophisticated graphics processing units (GPUs) especially from NVIDIA Corporation with the CUDA parallel computing platform made superior computation power available for broad application. Moreover, among the large organizations like Google, Microsoft, or Facebook the conviction has grown that the machine learning algorithms themselves are not valuable but the main resource is the required data to train the machine learning algorithms and the expertise about potential applications.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Hypothesis: Machine Learning algorithms can be trained to analyze radiological breast imaging data with the same accuracy compared to human readers, particularly radiologists.

Primary objective: Determine the accuracy of different machine learning techniques in the analysis of radiological breast imaging data and compare the accuracy with human readers.

Secondary objective: Compare different machine learning algorithms regarding their performance for different aspects (image quality, breast tissue density, presence of benign and malignant lesions) in the evaluation of radiological breast imaging data (mammography, breast-CT, ultrasound, and breast-MRI).

2.2 Primary and secondary endpoints

The variable of primary interest is the accuracy of machine learning algorithms for the detection of breast cancer. Patient specific factors may have an influence on the machine learning accuracy such as type of breast cancer, stage of the disease, breast density, age, and weight. Moreover, different breast imaging techniques exhibit differences in sensitivity and specificity; therefore the chosen breast imaging modality will show influences on the achievable machine learning accuracy. Finally, the amount of available data and the type and parameters of the machine learning algorithms themselves will show substantial influences on the maximum achievable accuracy. Therefore, the comparison of different machine learning algorithms for different radiological breast imaging modalities is a secondary endpoint of the study.

2.3 Project design

This is a multi center research project in which already existing health-related personal data is further used for research. A retrospective study design will be applied using data from the PACS image archive of the University Hospital Zurich and Kantonsspital Aarau. Systematically, the accuracy of machine learning algorithms for the classification of aspects of breast imaging (depiction of cancer, image quality, breast density,…) in different imaging modalities (mammography, ultrasound, breast-MRI, breast-CT) will be evaluated. The accuracies will be determined on the data used for training of the machine learning algorithm as well as on the validation datasets. Where appropriate (e.g. cancer detection), the accuracies will be compared to human reading in a small test cohort of maximum 200 cases. Post-processing and reading of

the images will be performed in consensus by at least two of three experienced radiologists and histological data will be used as the reference standard.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

In this retrospective study, the project population consists of all patients have obtained radiological breast examinations in the years 2009-2021 with respective imaging data stored in the PACS archive of the University Hospital Zurich and the Kantonsspital Aarau. Inclusion criteria are: radiological breast imaging data in the PACS archive, exclusion criteria are: age below 18 years, disagreement to the use of clinical data in the general consent.

In most of cases before the year 2016 and which did not receive imaging examinations after 2016 at the USZ and KSA, no participant consent will be obtained because it would be disproportionately difficult to obtain it or to provide information on the right to dissent since most of the patients are not attending our hospitals at the moment. Moreover some of them died and to exclude those cases would represent a bias for the study. No documented refusal is available for all of them. The interests of research outweigh the interests of the persons concerned in deciding on the further use of her data since the project aims to analyze multiple aspects that could be helpful for a better understanding of breast cancer disease and its diagnosis in the future. Many women may benefit from the results of this study.

For all imaging data acquired after 2016, only those images will be included in the study, for which a signed general consent is available agreeing to the scientific evaluation of the data.

All available imaging data in the time period from 2009-2015 comprises at USZ 24.288 mammographies, 22.092 breast ultrasound examinations, 1.988 breast MRI examinations, whereas at KSA 23.940 mammographies, 26.049 breast ultrasound examinations and 2.429 breast MRI examinations. The number of corresponding patients can only be estimated as multiple examinations may occur from the same patient, and the number of different patients cannot easily be determined from the databases. It may be estimated to 10.000 different patients at each institution. The database of KSA allows to obtain the number of died patients from the patients with breast imaging examinations between 2009 and 2015, which is 1.021. At USZ such data is not available, however from the mortality of patients in the estimated age of 60 at an imaging examination between 2009 and 2015 of 5% (Schweizerisches Bundesamt für Statistik), at least 500 patients at USZ have died.

3.2 Recruitment, screening and informed consent procedure

Please refer to paragraph 3.1

3.3 Study procedures

All imaging and health-related personal data is stored in PACS, RIS and KISIM, respectively. Imaging exams and histological data may be reviewed.

Persons who are entitled to pass on the personal data: only persons involved in the study (A. Boss, MD; M. Marcon, MD; N. Berger, MD; T. Schnitzler, MD; S. Laures, MD; S. Kelemen, MD; A. Cornelius, MD; F. Burn, MD; S. Schindera, MD).

Persons who are entitled to receive the personal data: only persons involved in the study (A. Boss, MD; T. Frauenfelder, MD; M. Marcon, MD; N. Berger, MD; Alexander Ciritsis, PhD, Patryk Hejduk, MSc; Karol Borkowski; PhD; T. Schnitzler, MD; S. Laures, MD; S. Kelemen, MD; A. Cornelius, MD; F. Burn, MD; S. Schindera, MD).

Person who are responsible for protection of the data disclosed: A. Boss, MD (USZ); S. Schindera (KSA).

Persons who are entitled to access rights for the health-related data: only persons involved in the study (A. Boss, MD; M. Marcon, MD; N. Berger, MD; T. Schnitzler, MD; S. Laures, MD; S. Kelemen, MD; A. Cornelius, MD; F. Burn, MD; S. Schindera, MD).

Breast imaging data from different radiological breast imaging modalities (conventional mammography, breast ultrasound, breast-MRI and breast-CT) will be automatically retrieved from the PACS archive of the University Hospital of Zurich as well as Kantonsspital Aarau and linked to the report from the RIS archive. In the database query, those patients disagreeing to the scientific use of their clinical data based on the general consent of the USZ and KSA (which is mandatory to fill in for all patients since the year 2016) will be omitted.

3.4 Withdrawal and discontinuation

Not applicable.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

We expect a total sample size of about 20.000 patients. This is the expected number of patients for whom imaging studies should be available. We chose to analyze a time interval of 12 years (2009- January 2021) to achieve as much as possible homogenous information from imaging studies according to the technique and protocols available for breast imaging examinations. The more data, the better machine learning algorithms will perform. A minimum number of about 50-70 cases will be included for each subgroup for additional imaging evaluation.

4.2. Handling of missing data

Not applicable.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [11], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [9] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21 [9].

5.4 Procedure for investigations involving radiation sources

Not applicable.

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants. Substantial amendments are changes that affect the safety, health, rights and obligations of project participants, changes in the protocol that affect project objective(s) or central research topic (category B only), changes of project site(s) or of project leader and sponsor. Note: List of substantial changes is available on www.swissethics.ch.

5.6 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

5.7 Insurance

Not applicable.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

In this project, we will evaluate the potential improvement of breast cancer detection using techniques of machine learning. Moreover, we will identify risks in the combination of machine learning with different imaging modalities in which the application of machine learning algorithms for the detection of breast cancer might not be reliable. From the intended results, we expect strategies for improved breast cancer detection in the future as well as information, in which applications the patient might be exposed to risks using machine learning techniques for cancer detection.

6.2 Risk-Benefit Assessment

All the collected data and information will be stored and processed in coded form in order to minimize the risk of unwanted identification of project participants (please refer to paragraph 7.2 below). The study does not aim to obtain immediate benefit for the project participants but to analyze multiple aspects that could be helpful for a better understanding of breast cancer disease and its diagnosis in the future using machine learning techniques.

6.3 Rationale for the inclusion of vulnerable participants

Not applicable.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Patient data will be collected, evaluated and stored exclusively in the hospital internal system. For imaging evaluation, workstations routinely used for ultrasound and MR examinations will be used. Externally, only coded data will be disclosed without personality traits (except sex and age). Health related personal data will be collected from the hospital patient information system

(KISIM) and stored in a secure access hospital internal server. This list serves as the basis for evaluating imaging data from the hospital internal system as well as for the collection of clinical and histopathological information. A new completely coded list is generated from these data and every patient corresponds to a case number, including information about patient's gender and age. The case number key is stored along with the original, non-coded list, in a secure access hospital internal server. Further data processing and statistical analysis are performed on the basis of coded data. There will be no data concerning patient information outside the hospital. Only the coded information from the evaluations is passed on to further processing and statistical analysis. Particularly, machine learning algorithms will be fed only with coded data. Imaging data will not be exchanged between the two participating two institutions, but instead machine learning models will be trained independently in both institutes. The AI models, which have no meaning regarding original patient data any more, can be pooled by transfer learning or federated learning. The study data will be kept for 10 years. The patient data from PACS, RIS and KISIM remains in the system in accordance with the legal guidelines. An excel sheet will be used to record the data and to create the database. The database will be stored in a folder on a secure access hospital internal server. For tracing unauthorized and accidentally determined changes of the analyzed data a copy of every version will be saved after each update as a password-protected excel file. The password is only known by the project leader.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. Data generation, transmission, storage and analysis of health related personal data within this project will follow strictly the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Health related personal data evaluated during this project from participants are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality. Data protection: project data will be handled with uttermost discretion and only be accessible to authorized personnel. Direct access to source documents will be permitted for purposes of monitoring, audits or inspections and only the investigators involved in the study have access to project plan, and dataset, during and after the research project (publication, dissemination).

7.4 Retention and destruction of study data and biological material

There will be no data concerning patient information outside the hospital. Only the coded information from the examinations is passed on to further processing and statistical analysis. The study data will be kept for 10 years. The patient data from PACS, RIS and KISIM remains in the system in accordance with the legal guidelines. An excel sheet will be used to record the data and to create the database. The database will be stored in a folder on a secure access hospital internal server. For tracing unauthorized and accidentally determined changes of the analyzed data a copy of every version will be saved after each update as a password-protected excel file. The password is only known by the project leader.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The project participants declare that they have no conflict of interest. Funding is provided by the Department of Interventional Radiology (USZ) and the University Zurich (UZH).

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