Study Protocol for FAST MRI: Diagnostic Yield study for Average MammOgraphic screeNing Density

FULL/LONG TITLE OF THE STUDY	Diagnostic yield study to determine whether an abbreviated form of breast magnetic resonance imaging (FAST MRI) can detect breast cancers missed by screening mammography: for women at population risk of breast cancer with average mammographic density following their initial screening mammogram
SHORT STUDY TITLE / ACRONYM	FAST MRI: Diagnostic Yield study for Average MammOgraphic screeNing Density (DYAMOND)
RESEARCH REFERENCE NUMBERS:	5273
PROTOCOL VERSION NUMBER:	3.0
DATE:	21st June 2024
IRAS project ID:	330059
SPONSOR:	North Bristol NHS Trust ResearchSponsor@nbt.nhs.uk
FUNDING:	Efficacy and Mechanism Evaluation (EME) Programme
	NIHR150502

This protocol has regard for the HRA guidance and order of content.

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):.....

(Please see separately uploaded signed page)

KEY STUDY CONTACTS

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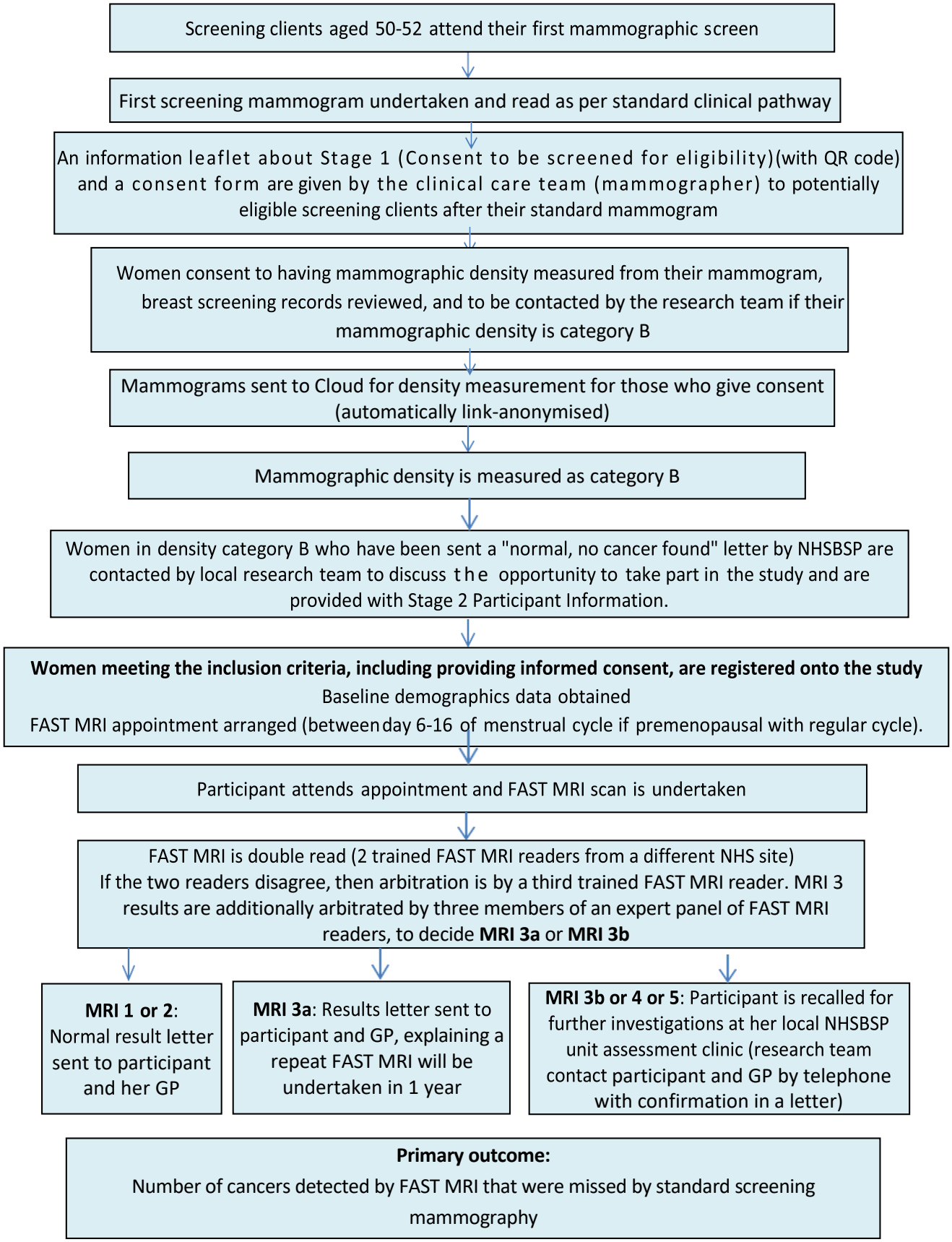
Funder	NIHR Efficacy and Mechanism Evaluation (EME) Programme
Key Protocol Contributors	Lyn Jones, Rebecca Geach, Janet Dunn, Andrea Marshall, Sian Taylor-Phillips, Sam Harding, Abeer Shaaban, Sadie Mckeown-Keegan, Abi Loose, Mark Halling-Brown, Sarah Vinnicombe, Janice Rose, Helen Matthews
Committees	Programme Steering Committee (PSC), Trial Steering Committee (TSC) and Trial Management Group (TMG)

TRIAL SUMMARY

Study Title	Diagnostic yield study to determine whether an abbreviated form of breast magnetic resonance imaging (FAST MRI) can detect breast cancers missed by screening mammography: for women at population risk of breast cancer with average mammographic density following their prevalent (first) screening mammogram
Study Design	A prospective, multicentre diagnostic yield, single arm study with internal pilot (for recruitment etc.).
Study Participants	Women aged 50-52 years who have been invited for their first (prevalent) mammogram screening. Women of average breast density (BIRADS category B)
Planned Size of Sample (if applicable)	1000
Follow up duration (if applicable)	All women will have their screening records (NBSS) followed up and the local cancer registries will be interrogated by the local teams during the study. Participants who had an MRI 3a FAST MRI result, and also those who had an MRI 3b, 4 or 5 result but no cancer diagnosed at biopsy will be invited back for a second FAST MRI scan after 1 year.
Planned Study Period	42 months
Research Outcome(s)	The primary outcome is the number of cancers missed by mammography but detected by FAST MRI. Secondary outcomes include the grades, sizes and stages of cancers detected, recruitment rates, recall rates, biopsy rates, any adverse reactions to FAST MRI and intervention acceptability to participants.

FAST MRI: Diagnostic Yield study for Average MammOgraphic screening Density (DYAMOND)



FUNDING AND SUPPORT IN KIND

FUNDER	NIHR Efficacy and Mechanism Evaluation (EME) Programme
Total grant	**£1,360,474.58**

ROLE OF STUDY SPONSOR AND FUNDER

North Bristol NHS Trust Research and Innovation Department has overall responsibility for the initiation and management of the study.

North Bristol NHS Trust Research and Innovation Department has had no role in the design of the study and will not play a role in the study conduct, data analysis and interpretation, manuscript writing, and dissemination of results. These aspects of the study will be decided by the researchers and the sponsor will oversee compliance with governance procedures.

The funder, NIHR Efficacy and Mechanism Evaluation (EME) Programme, is providing the finance for the project.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Organisation

Trial Management Group (TMG)
A formal Trial Management Group will confer remotely on a monthly basis to ensure the study is progressing effectively and on schedule and will comprise the Project Manager and the grant co-applicants. Other members of the research team will be involved in the meetings as required, depending on the stage of the study. Informal communication between the CI, Joint CI and project manager will occur daily. The lay member of the study team, if unable to attend a TMG, will be updated on study progress through the circulated minutes and on a bi-monthly basis at the regular programme meetings, so that regular updates can be fed back to service users.

Trial Steering Committee (TSC)
A formal Trial Steering Committee (TSC) will be formed to provide overall supervision for the project on behalf of the study's Sponsor and Funder and to ensure that it is conducted to the rigorous standards set out in the UK Policy Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

There will be at least 8 voting members of the TSC, reviewed and invited by the NIHR EME Programme Director. This will include at least 6 independent members, including an Independent TSC Chair, an independent statistician, an independent public and patient representative and independent professionals from disciplines related to the study. It is planned that the CI (deputised by the Joint CI) and a second patient representative who was a lay co-applicant for the grant but is not part of the TMG will be proposed as the 2 non-independent members. The TSC will invite observers to its meetings, including the Trials Manager for the study, representatives from Sponsor, from the CRN and from the involved CTU (Warwick).

The TSC will meet approximately 6 monthly and at least annually throughout the grant.

In summary the TSC will:

- Provide advice, through its Chair, to the study's funder, sponsor, Chief Investigator, host institution, and contractor
- Concentrate on the study's progress, adherence to the protocol, and patient safety (where appropriate), and to consider new information of relevance to the research question
- Uphold the rights, safety and well-being of the participants: these are the most important considerations and should prevail over the interests of the research
- Ensure appropriate ethical and other approvals are obtained in line with the project plan
- Agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- Provide advice to the investigators on all aspects of the study
- Maintain oversight of the study objectives
- Receive updates from the Data Management and Ethics Committee (DMEC) and from the researchers and make decisions regarding the study/grant
- Identify and agree milestones, and to monitor and supervise the progress of the study/grant against these
- Maintain financial oversight and financial plans to keep spending on target
- Encourage appropriate efforts to disseminate the programme's findings, including the timely provision of
    - the final report and
    - the development of articles for submission to academic journals
- Consider and advise on the implications for the research of any new evidence from both within the programme and other sources, or of any proposed changes to the programme.

Data Management and Ethics Committee (DMEC)

A formal independent DMEC will be formed to safeguard the interests of DYAMOND study participants, assess the safety and efficacy of the intervention during the trial, and to monitor the overall conduct of the DYAMOND study. The DMEC will report its findings to the TSC, the Chair of the TSC, the Chief Investigator and to the TMG.

The DMEC will receive and review the progress, and the accruing data, of the DYAMOND study and provide advice on the conduct of the study to the Trial Steering Committee (TSC).
The DMEC should inform the Chair of the TSC if, in their view: the results are likely to convince a broad range of clinicians, including those supporting the study and the general clinical community, that the intervention, for all or a subset of study population, is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence screening client management.

The specific role of the DMEC is to conduct Interim reviews of the trial's progress including updated figures on recruitment, data quality, and main endpoints including safety data.

Public Involvement

Our collective Public and Patient Involvement and Engagement (PPIE) contributors' personal experiences guided and challenged the research team during the proposal's development, working collaboratively to ensure the proposal's importance and relevance for women.
PPIE has been integral in the planning of the research question and study design:

- The FAST MRI programme's core aim is to reduce the number of breast cancers diagnosed at a late stage through being undetected on a mammogram. Input from women living with metastatic lobular cancer (diagnosed late due to masking on mammogram) emphasised the human cost of late diagnosis.
- Breast Density Matters UK, campaigns for supplemental screening for women with high mammographic density. They understand that there is a knowledge gap about whether FAST MRI could find cancers missed by mammography for women with average density. They acknowledge that the exclusion of women with high mammographic density from this proposal is a necessary step in the optimisation of breast screening for all.
- Our PPIE contributors highlighted the importance of keeping MRI scan times short and that the absence of ionising radiation is an important advantage of FAST MRI over mammography. They expressed their appreciation of the fine balance of risk vs. benefit in breast cancer screening. The clinicians and PPIE members discussed the literature and estimates of false positive biopsies from FAST MRI and collaboratively developed the proposal's strategy for dealing with MRI 3 (uncertain) results.

Ongoing PPIE will include the formation of a formal PPIE group, comprising the 2 PPIE co-applicants on the grant and 6 other PPI representatives.

The following PPIE activities will be undertaken by at least the two PPIE co-applicants and the grant PPIE Lead:

- Ensuring the study protocol is feasible, inclusive and accessible to study participants.
- Leading discussions with the wider FAST MRI PPIE network to design an infographic/visual recruitment flyer and a short video (explaining the study) – these will be the initial study information provided to potential participants. This flyer and the video will enable us to optimise engagement with women, including those who may not otherwise attend their screening appointment.
- Co-design the participant information, including the formal information sheets, to ensure they are accessible and inclusive.
- One of our two Lay Co-Applicants will be a member of the monthly TMG meetings, ensuring public and patient views are represented in all aspects of study delivery and operational oversight. The other will be a member of the TSC.

- Leading the evaluation of our results by the public through our formal PPI group and also through Independent Cancer Patients Voice (ICPV), National Cancer Research Institute (NCRI) Breast Group, Breast Density Matters UK and the Bristol Breast Cancer Unit Support Trust, BUST.
- Leading public dissemination of the study's progress and results, ensuring communications, publications and presentations are accessible and engaging. ICPV will be actively involved in the dissemination of the study results.

The PPIE Lead will be responsible for ensuring that involvement is aligned to UK Standards for Public Involvement including communicating to public contributors the project status and providing feedback on PPIE activities and their impact. The PPIE Lead will oversee the development and implementation of appropriate evaluation, monitoring and reporting of PPIE. Formally this evaluation will use a PPIE impact log and GRIPP2 guidance. Informal adaptions, and field notes will be kept to supplement feedback, and provide additional colour to our interpretations and application to future work.

KEY WORDS: **Breast cancer, screening, early diagnosis, imaging biomarker, FAST MRI, abbreviated MRI,**

Table of Contents

ii. LIST OF ABBREVIATIONS

ACR	American College of Radiologists
AE	Adverse Event
AI	Artificial Intelligence
AR	Adverse Reaction
BI-RADS	The ACRs' Breast Imaging Reporting and Data System
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DCE-MRI	Dynamic Contrast Enhanced breast MRI
DMEC	Data Monitoring and Ethics Committee
FAST MRI	First post-contrAst SubtracTed breast MRI
FAST MRI protocol images	Information given to the MRI scanner to acquire the FAST MRI
fpMRI	Full protocol breast MRI
GCP	Good Clinical Practice
H&E	Haematoxylin and Eosin
HBRC	University of Birmingham Human Biomaterials Resources Centre
ICF	Informed Consent Form
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MRI	Magnetic Resonance Imaging
NBSS	National Breast Screening Service database
NBT	North Bristol NHS Trust
NHSBSP	National Health Service Breast Screening Programme
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIL	Participant Information Leaflet
PIS	Participant Information Sheet
PPIE	Public and Patient Involvement and Engagement
PSC	Programme Steering Committee
RCT	Randomised Controlled Trial
RIDAC	NHSBSP Research Innovation and Development Advisory Committee
REC	Research Ethics Committee
RSH	Royal Surrey Hospitals NHS Foundation Trust
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
TILs	Tumour Infiltrating Lymphocytes
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Group

1 BACKGROUND

1.1 Scientific Summary

Despite effective treatments, 30 women die from breast cancer every day in the UK(1). Early diagnosis of breast cancer saves lives(2) and is the aim of the NHS Breast Screening Programme (NHSBSP) which offers mammographic screening to women aged 50-70 years every 3 years. The NHSBSP screens 2.12 million women in England each year (3) and confers a 20% mortality benefit to women invited for mammographic screening(4). However, screening benefit must be weighed against any harm caused and, for mammographic screening, there is a fine balance of benefit and harm(5–7).

Mammographic screening programmes, including NHSBSP, result in disputed levels of overdiagnosis (detection of cancers which would not have caused harm during a woman's lifetime), and also fail to prevent a continued incidence of stage 2-4 breast cancers (underdiagnosis))(4,7) and of interval cancers(8) (which present symptomatically between screening rounds and comprise 30-44% of all breast cancers within the NHSBSP screened population(8–10). Both overdiagnosis and underdiagnosis contribute to the harms of mammographic screening. Overdiagnosis leads to morbidity from overtreatment. Underdiagnosis causes delayed breast cancer diagnosis and a worse prognosis with a much higher chance of the morbidity of living with metastatic breast cancer and its treatment, and ultimately of mortality(2). It has been estimated that 35,000 people in the UK are living with metastases and the knowledge that their breast cancer is incurable(11).

FAST MRI (First post-contrAst SubtracTed Magnetic Resonance Imaging) has potential as a breast cancer screening test (12). It overcomes the shortcomings of mammography, including poor sensitivity for aggressive cancers(12–15). FAST MRI is much quicker to acquire and interpret (cost benefit) than the gold standard breast screening modality, full protocol MRI (fpMRI), which is currently reserved to screen only women at high risk of breast cancer (3,16,17) FAST MRI holds promise to save more lives through breast cancer screening because it can detect aggressive cancers earlier than mammography (12,14).

Research suggests FAST MRI has similar diagnostic accuracy of cancer detection to fpMRI but notes that the considerable variation in MRI protocols used by the studies reviewed reduced the quality of the evidence provided (14,18). Since these studies a FAST MRI protocol has been developed by the FAST MRI Programme team during the OPERA study, (19), optimising the sequence parameters to standardise different aspects of image quality across different models and manufacturers of MRI scanner and defining acquisition timing. (19)

We will invite volunteer participants of screening age to have a FAST MRI scan to test the sequence parameters derived from the OPERA Study. This will form the Quality Assurance phase of DYAMOND and aims to identify any issues with the scanning / acquisition protocols before participants are recruited to the main study.

We will invite screening clients who attend for their first mammogram (50-52yrs) who have an average breast density (measured by an automated AI tool) to be part of 1,000 women to have a FAST MRI scan at multiple sites in England.

All women will have their screening records followed up at 6-month intervals during the study and the local cancer registries will be interrogated at 6-month intervals by the local teams during the study.

Participants who have a FAST MRI 3a result and those who had a FAST MRI 3b, 4 or 5 result but a biopsy that did not show cancer will be invited back for a second FAST MRI scan after 1 year. Whether a FAST MRI 3 result is classified as FAST MRI 3a or 3b will be decided by an expert panel of MRI readers. This plan for dealing with FAST MRI 3 results within the study has been reviewed and approved by the NHS Breast Screening Programme Research Innovation and Development Advisory Committee (NHSBSP RIDAC).

1.2 Plain English Summary

Finding breast cancers early saves lives.

The NHS Breast Screening Programme uses either mammograms (quick x-rays) or MRI scans to help find breast cancers. Mammograms are used most widely as they can be done quickly, but small cancers can sometimes be hidden by breast tissue. MRIs are better at detecting these small cancers, but they are expensive, so are only offered to people at highest risk of developing breast cancer.

A newer type of scan is the "FAST" MRI. They are quick like mammograms and may be better at detecting small cancers like MRI.

The DYAMOND study will test if a FAST MRI scan can detect cancers not seen on mammogram, in women with average density breasts.

1000 women will be invited for a FAST MRI if:
- they are aged 50-52,
- their mammogram is clear
- their breast density is "average" (a computer measures this from mammogram images)

The FAST MRI scans will be checked by trained health professionals. If any cancers are found, the women will be looked after by their local hospital, and information about their care will be collected for the DYAMOND study.

We will ask women what they thought about having the FAST MRI scan to see how acceptable it is to them.

If this study shows that cancers missed on a mammogram can be seen on a FAST MRI for women with average density breasts, we will carry out a larger study to see if FAST MRI may be a good alternative to mammograms for breast screening. We will share the findings with the public, health professionals and other researchers.

We are working with breast cancer support groups and women with experience of breast cancer and breast screening to make sure the patient voice is listened to throughout this study.

2 RATIONALE

To address the problem of underdiagnosis inherent in mammographic screening, researchers have proposed the development of risk-stratified approaches to population breast screening; a supplemental more sensitive screening test is offered, in addition to mammography, to the subset of the population most likely to have a breast cancer missed by mammography (20–22). The use of mammographic density to define this subset for supplemental screening has been recommended, because women with denser breasts have both a higher risk of developing breast cancer and a greater risk of their cancer being missed on mammography (23–25)]. In the UK, the American College of Radiologists' Breast Imaging Reporting and Data System (BI-RADS) classification is used to define breast composition(26) . BI-RADS classifies breast composition into 4 density categories: A, B, C and D, where A is the least dense category and D the densest. At the age of first mammogram for population screening within the NHSBSP (50-52 years) the percentage of women in each density category is approximately A:10%, B:40%, C:40% and D10%% (26) . Density determined risk adaptive strategies suggest supplemental screening either for women with category D breasts or for those in both categories C and D(20,25,27,28).
The explanation for both overdiagnosis and underdiagnosis lies in the diversity of breast cancer biology and mammography's unfavourable sensitivity profile for cancer detection. Some indolent, biologically irrelevant cancers are well shown on mammograms but are unlikely to cause harm, while other aggressive, biologically relevant cancers are typically not well shown on mammograms but are likely to progress to stage 2-4 disease if left untreated (15,29–32). There is also some evidence that the mortality benefit conferred by screening is predominantly from high grade cancers, particularly grade 3, which are frequently missed by mammography (33).

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of the breast is the essential component of the standard breast MRI used in clinical practice(34). It is a more sensitive test for breast cancer than either mammography or digital breast tomosynthesis (DBT), able to detect aggressive cancers early and thereby reduce the incidence of interval cancers to 0-5%(13,28,32). In addition, in a screening trial for women with mammographically dense breasts (Ds), supplemental DCE-MRI reduced the incidence of Stage 2-4 cancers at the subsequent screening round to zero(35). DCE-MRI is the standard screening test within NHSBSP for women at high risk of breast cancer (>30% lifetime risk or ≥ x 8 relative risk to population) in whom it has been shown to confer a survival benefit (16). However, it is expensive, time consuming (both to acquire the images and to report the findings) and it requires highly trained image readers for its interpretation. For these reasons it is unsuitable as a mass-screening test (tariff costs used at our centre are £178 for DCE-MRI (May 2023) and £56 for a mammogram).

To reduce breast cancer mortality, we need a cost-effective screening tool that will preferentially find the aggressive cancers that are not well seen on mammograms. This was highlighted by Public Health England in the 2015 Report of the Working Party for Higher Risk Screening(36). Ideally the test will also result in less overdiagnosis than mammography and be at least as quick to acquire (acceptability and cost) and to report (cost and workforce capacity) as mammograms. A type of abbreviated/shortened MRI of the breast, called FAST MRI(12), has been suggested for this role (14,37–39). Previous studies have shown that expert image readers take less than a minute to correctly interpret each FAST MRI examination (12,14,18,40–43).

Research shows that, to interpret FAST MRI, NHSBSP MRI readers take a median time of 33 seconds (range 3-351 seconds) and NHSBSP mammogram readers take a median time of 75 seconds (range 10-416 seconds) following a single day of standardised training(43,44). This is comparable with published times taken by experienced UK mammogram readers to interpret screening mammograms (35 seconds(45)).

Research teams worldwide have focussed recently on offering supplemental/additional imaging (e.g. with FAST MRI) only to the subset of women with high mammographic density (D only or C and D)(20,25,27,28,46), and the UK National Screening Committee, which advises the four UK governments on screening policy, recently investigated density measurements for use in identifying women for further testing (47). However, women with category B mammographic density (40% of the population at first NHSBSP screen (26) can also have their

cancers missed by mammography because mammograms are not good at showing some types of cancers (including lobular carcinomas(30) and small, grade 3 aggressive cancers(15)).

This study will determine whether FAST MRI could detect early aggressive breast cancers, missed by screening mammography, in women with average breast density (category B(26)). This would inform future research trial design by determining whether an approach inclusive of women with category B breasts would be worth pursuing in the quest to save lives through early detection of breast cancer.

2.1 Assessment and management of risk

This trial is categorised as:

- Type A = No higher than the risk of standard medical care
- **Type B = Somewhat higher than the risk of standard medical care**
- Type C = Markedly higher than the risk of standard medical care

The potential risks to participants in this study (and our mitigations for those risks) include:

1. Risk and adverse impacts from having a FAST MRI
    1. Background:
        - FAST MRI is a component of fpMRI, which is standard procedure in the UK as a breast cancer screening test for women at high risk of developing breast cancer. FpMRI is also used as an imaging test in standard UK clinical practice to stage breast cancer prior to neoadjuvant chemotherapy and for lobular cancers prior to surgery, to assess response to neoadjuvant chemotherapy and to troubleshoot diagnostic uncertainties (17)
        - Like fpMRI, and MRI tests routinely used to image many other parts of the body, FAST MRI involves the intravenous injection of gadolinium-based contrast agent (GBCA). The type of GBCA that will be used in this study is macrocyclic GBCA. The dosage will be standardised across recruiting sites and will be the lowest dose to provide adequate enhancement of the study intervention.
        - The safety profile of macrocyclic GBCA is well documented and radiology departments administer them to patients and screening clients on a daily basis in the UK
        - Guidance on their administration is available from the Royal College of Radiologists website: https://www.rcr.ac.uk/publication/guidance-gadolinium-based-contrast-agent-administration-adult-patients and this guidance is followed in UK radiology departments whenever GBCAs are administered, including during research studies (48)
        - The European Medicines Agency has published a pharmacovigilance risk assessment report on GDCA use (49)
        - Safety Guidance for Magnetic Resonance Equipment in Clinical Use was published by the MHRA in February 2021 and is available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/958486/MRI_guidance_2021-4-03c.pdf
    2. In summary:
        - Magnetic Resonance Imaging, with and without the intravenous administration of GBCAs is carried out on patients and screening clients at hospitals across the UK every day as part of standard care.
        - The type of GBCA administered in this study will be macrocyclic GBCA. The dosage will be standardised for each MRI scanner within the study and will be the lowest dose to achieve adequate enhancement of the study intervention.
        - GBCAs are associated with a very low rate of immediate adverse events (0.06%-0.09%),
        - Most adverse events are mild and can be managed in the radiology department.

- Major life-threatening contrast reactions to GBCAs are extremely rare. The incidence of acute, severe reactions is estimated to be 0.0025-0.005%
- Tiny amounts of GBCA can be retained in the brain with repeated administration, although this is much less for macrocyclic than for linear GBCAs. The long-term clinical consequences of this retention are unknown although it has been extensively investigated and studies to date have been reassuring.

3. In addition to the small risk from GBCA administration, people can be adversely impacted by the following relating to any MRI scan, including FAST MRI
    - Anxiety relating to the environment (very technical/medicalised/hospitalised setting)
    - Discomfort from the placement of an intravenous cannula prior to the scan and its removal after the scan. This is necessary to administer the GBCA.
    - Feelings of claustrophobia during the scan (entails lying in a noisy tunnel during the scan).
    - Our research team undertook PPI work on breast MRI acceptability which helped us to understand that prior knowledge of what having a breast MRI is like is useful to minimise anxiety and so we developed a short film to explain the process of fpMRI. As part of this Grant, we will be updating the film to make it specific for FAST MRI and we will make it available on our trial website.
    - The PPI work also identified that explaining the scan duration to participants (approximately 3 minutes for a FAST MRI) will help to minimise any feelings of claustrophobia.

2. In addition to the risks and adverse impacts from having a FAST MRI, study participants may experience an adverse impact from feeling anxious whilst they are having to wait for the following:
    1. The results of the FAST MRI scan (for all participants)
    2. The repeat FAST MRI in 1 year (for a subset of participants with an MRI 3a result, estimated at 31-57 participants in total (3.1% from Bakker et al 2019 (28)and 5.7% from Kuhl et al 2017(13)) who will receive a FAST MRI results letter inviting them to have a repeat FAST MRI in 1 year

    We plan to minimise these potential adverse impacts through careful writing (jointly with our PPI group and Lay Researchers) of the participant-facing documents, including the PIS and the letter to women with MRI 3a FAST MRI result. Additionally, the local researcher will talk through all possible results of the FAST MRI and their implications prior to taking consent for the FAST MRI scan.

3. For the subset of participants who have a FAST MRI result MRI 3b, 4 or 5 (estimated at 44-64 participants in total (4.4% from (13)and 6.4% from Bakker et al 2019(28)), there is likely to be anxiety and distress when they receive their FAST MRI results phone call from the local researcher explaining that they will need to attend a breast assessment clinic at their local breast screening service where they will have a breast examination, a mammogram, a breast ultrasound and a biopsy because their FAST MRI scan suggests that further investigation is necessary to exclude a cancer.
    1. We anticipate all 44-64 of this subset of participants will experience anxiety/distress at the subsequent clinic visit and discomfort at the time of their breast biopsy. The anxiety associated with a clinic recall is already experienced by clients recalled from their standard screening mammograms and so as to prevent individuals suffering this twice, being recalled from standard screening mammogram is an exclusion for this study. The time between the phone call informing the participants of the need to attend an assessment clinic for further investigations and the clinic appointment is likely to be no more than 2 weeks.
    2. Of this subset of participants (44-64 women), we expect 16-23 of them to have a cancer found at the subsequent biopsy (from 1.6% in Bakker et al 2019(28) to 2.3% Kuhl et al 2017 (14))
    3. We will invite the remaining members of the subset of participants with an MRI 3b, 4 or 5 FAST MRI result (21-48 participants in total), those who did not have a cancer found on biopsy at the assessment clinic, for one further FAST MRI at y1. This subset may experience further anxiety

and distress during the year until they receive their second FAST MRI and their second FAST MRI result at y1.

The potential benefits to participants in this study include:

1. The subset of participants who have a breast cancer detected by FAST MRI and confirmed by biopsy, estimated 16-23 participants in total (from 1.6% in Bakker et al 2019(28) and 2.3% in Kuhl et al 2017 (14)) will have had their cancer detected earlier than if they had not been a participant. Although this is likely to cause them considerable distress and morbidity from treatment of the cancer, it is likely to reduce the treatment associated morbidity in comparison with if the cancer had been left undetected until a later date. Due to the earlier detection of the cancer, it is also likely that their survival from breast cancer and that their overall survival will be improved as a result of their participation in the study (2,16,50).

Risks to participant data and assessment of those risks are listed in the table below (on a scale of 1-5, 1 is the minimum and 5 is the maximum) along with details of risk mitigation measures taken:

	Describe the source of risk and nature of potential impact on individuals. Include associated compliance and corporate risks as necessary.	**Likelihood of harm**	**Severity of harm**	**Overall risk -**
1	Unauthorised access to FAST MRI image database / repository risk reduced by comprehensive cloud security measures implemented	*1*	*5*	*5*
2	Patient identifiable information left in standard DICOM tags. Risk reduced by comprehensive compliance with DICOM supplement 142	*1*	*5*	*5*
3	Patient identifiable information left in private DICOM tags reduced by all private tags stripped	*1*	*5*	*5*
4	Images stolen from cloud location. Risk reduced by comprehensive cloud security measures implemented	*1*	*5*	*5*
5	Images deleted from cloud location. Risk reduced by deletion versioning and retention activated	*1*	*5*	*5*

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of this research is to refine the study design, and define the study population, for a future randomised controlled trial (RCT) of FAST MRI as a screening modality for women having their first mammographic screen with NHSBSP (future application to NIHR). Specifically, the proposed work will determine if women with average mammographic density (BI-RADS category B) could benefit from screening with FAST MRI and fill the knowledge gap.
The hypothesis this proposal will test is that FAST MRI can detect breast cancers missed by mammography for the 40% of the population of women having their first mammogram with NHSBSP (age 50-52) who have category B mammographic density. The findings of this study will be important, no matter whether the hypothesis is proved or disproved, because they will justify either the inclusion or the exclusion of 40% of the screened population (not previously investigated) in a future study proposal to NIHR (HTA) for a randomised controlled trial (RCT) of FAST MRI.

3.1 Primary objective

To measure the number of additional cancers detected by FAST MRI that were missed by screening mammography

3.2 Secondary objectives

• To assess the characteristics of cancer detected by FAST MRI (including grade, size, stage, nodal involvement and other characteristics linked to prognosis and benefit or harm from screen detection)
• To determine the acceptability of the intervention through questionnaire and an additional qualitative interview of a subset of participants
• To analyse recruitment rates, retention rates, recall rates, biopsy rates, early call rates and any adverse reactions to FAST MRI
• To streamline the prospective digital categorisation of mammographic density using NHS-owned (SciCom) software
• To determine the proportion of women in each density category (A, B, C, D) in the (UK) NHSBSP screened population at this age
• To create a dataset of mammograms and corresponding FAST MRI scans with known outcome having potential use in future training and research, for example for analysis with artificial intelligence/machine learning. A separate submission to the HRA will be submitted for this dataset.
• To collate a central pathology database of the cancers detected for future translational research
• To collect data to enable a micro costing exercise to extend the previously conducted Budget Impact Analysis(51)
• To explore data linkage for longer term outcomes

3.3 Outcome measures/endpoints

3.31 Primary endpoint/outcome

The primary outcome is the number of cancers that are detected on FAST MRI after a negative mammogram. This will be converted into a rate per thousand women screened to be comparable with current evidence.

Cancers detected by FAST MRI are for those participants whose FAST MRI scans were classified as MRI 3b 4 or 5 and who on subsequent investigation had a biopsy-confirmed breast cancer (invasive and non-invasive).

A sensitivity analysis will be undertaken to assess the need for the additional investigations for the MRI 3 group and whether MRI 3b and/or MRI 3a should be considered as cancers or negative results.

3.32 Secondary endpoints/outcomes

The secondary outcomes are:

- The characteristics of the cancers detected by FAST MRI (including grade, size, stage, nodal involvement)
- Acceptability of the intervention through questionnaire and an additional qualitative interview of a subset of participants
- Recruitment rate is defined as those that are recruited out of all those with density B that were contacted.
- Retention/compliance rate accounts for the number that withdraw from the study once recruited or do not attend the FAST MRI scan.
- Recall rate is defined as the proportion of women classified with a MRI 3b, 4 or 5 and invited for further investigation out of the total number of recruited women who had a FAST MRI.
- Biopsy rate is calculated as the number of biopsies undertaken out of all women recruited who had a FAST MRI,
- Early call rates is defined as the number of women who have a FAST MRI at y1 (includes all those classified as MRI 3, and those classified as MRI 4 and 5 who did not have cancer confirmed at y0 biopsy) out of all women recruited who had a FAST MRI at y0.
- Adverse reactions to FAST MRI
- Proportion of women in each density category (A, B, C, D) in the UK NHSBSP screened population at this age
- Interval cancers detected during the study period
- FAST MRI classifications of y1 scans (for all those with MRI 3a at y0 and those with MRI 3b, 4 and 5 and no cancer detected at y0).
- FAST MRI reader data, diagnostic accuracy of readers within the study (individually and by reader group and NHS site), numbers of scans requiring arbitration, standard arbitration outcomes and expert panel arbitration outcomes.

4 QUALITY ASSURANCE OF FAST MRI SCANS

Before research scans take place, the Central Quality Assurance (QA) team must be confident that the FAST MRI protocol has been optimised and standardised. This includes undertaking FAST MRI scans prior to the start of recruitment to the main study.

At least four scans will be undertaken by each site, per scanner type to ensure the acquisition protocol has been optimised for each type of scanner. The QA phase will stop once the FAST MRI protocol has been optimised.

Should the Quality Assurance team and/or Trial Steering Committee feel that the acquisition protocol needs further refinement, then a root cause analysis will be undertaken to understand why the number has needed to increase and to decide the most pragmatic way forward.

4.1 Recruitment to Quality Assurance (QA)

Participants will be approached independently from the Breast Screening Programme via social media, word of mouth and staff adverts (through email). Women interested in taking part will self-refer by following a link or QR code to register their interest. Once an expression of interest has been made by a potential participant, they will be given a Quality Assurance Participant Invitation Sheet and asked to complete the Quality Assurance Consent Form if they are interested in taking part. All participants will be given at least 24 hours to decide whether to take part and will be given opportunity to ask questions and have then answered satisfactorily. Consent will be received by a member of the local research team, using a paper consent form, a copy of which will be given to the participant, and one retained by the local research team.

Women will be of screening age to ensure background parenchymal enhancement will be no greater than for the participants within the main study. Additionally, QA participants will be familiar with the idea of breast cancer screening.

4.1.1 Inclusion criteria

- Aged 50-70
- Have had a screening mammogram within the last 3 years
- Have no previous history of a breast cancer diagnosis
- Do not belong to the group of women known to be at higher risk of breast cancer
- Willing and able to give remote fully informed consent
- No absolute contraindication to breast MRI

4.1.2 Exclusion criteria

- Aged <50 or >70
- Pregnant or breastfeeding
- Contraindication to MRI
- Unwilling to have FAST MRI
- Unwilling to allow follow-up of outcomes through data-linkage
- eGFR equal to or below 30
- BMI, weight and abdominal girth restrictions may apply to recruiting sites' MRI scanner(s) that could exclude otherwise eligible participants from having the study intervention

Participants found to have conditional contraindications to MRI will be reviewed by the local Radiology service and advice given as to the actions required to facilitate an MRI to take place, in line with local guidelines and best practice.

For example (but not limited to):

- participants who wear a continuous glucose monitor will be asked to remove the device for the scan appointment, or appointment scheduled for a time when sensor is due to be changed
- participants with a coil (Intra Uterine Contraceptive Device) will be asked to confirm the type to ensure it is not an absolute contraindication.

If it is not possible to reasonably adjust for the situation in question, by following local policy, the referral to FAST MRI will be rejected and the participant will not be eligible for a FAST MRI.

4.2 QA participant involvement, including FAST MRI scan

All standard MRI protocols will be followed including the completion of a safety checklist to ensure that there are no MRI contraindications. The scan will be booked at a time convenient to the participant by a member of the local research team. Following completion of the scan the participant will be asked to complete a brief qualitative survey. A proportion of the QA participants will be invited for a qualitative interview. Potential participants will be given a Qualitative Interview Participant Information Sheet and given as much time as they need to decide whether they would like to take part in the interview. Full details are described in section 8.

Upon completion of the qualitative survey (and optional qualitative interview), participation in the QA phase will be complete.

4.3 Reporting of QA scans

There should be a minimum of 2 Consultant Radiologists (LJ/RG/SV/LO'F) to interpret the FAST MRI scans. These should be reported within 5 working days of acquisition. Any incidental findings should follow the standard clinical pathway. The findings should be communicated with the participants through the standard FAST MRI DYAMOND protocol of research findings.

The quality assurance should be reviewed by the QA team against the criteria and a decision to proceed with the further QA scans or start study recruitment should be proposed to the Trial Steering Committee within 5 working days of scan acquisition.

4.4 QA Review Criteria

The QA Review Criteria should be followed to assess the quality of the scans and the outcome.

Up to 9 scans will be collected per scanner at each of the recruiting sites. These scans will be reviewed by the Quality Assurance team and will be graded to ensure they are of diagnostic quality. Any changes made to the sequence parameters will be retested. Scanners will be required to have passed the QA phase before being certified, and before participants to the main study can be recruited.

The QA team will review the answers given in the proforma for the first 3 scans to decide on their recommendation to the TSC. If they and the TSC decide that the FAST MRI protocol parameters need to be adjusted to improve scan quality, 3 further QA scans will be acquired prior to each subsequent QA team and TSC review until the detailed parameters of the FAST MRI protocol have been determined.

The outcome of the QA team review should be sent to the Trial Steering Committee whereby the final decision to start recruitment or continue with the QA scans should be decided within 8 working days of scan acquisition. The TSC Chair (or delegated TSC member) will review QA team recommendations and issue the final decision.

No DMEC review is required unless either the QA team or TSC feel that the outcome may affect the data or ethics of the trial. The outcome of the QA work will be included in the first DMEC report.

5 TRIAL SETTING

The FAST MRI DYAMOND study is a prospective, multicentre diagnostic yield, single arm study with an embedded qualitative study. All women recruited to Stage 2 will undergo a FAST MRI. An internal pilot will assess the willingness of sites and women to participate in the DYAMOND study.

A Fleming's two-stage design (52) will be used to assess the number of additional cancers detected by FAST MRI. This design allows for early stopping after stage one, which would save patients, funding costs and time continuing to the end of the study if the question could be answered earlier.

All sites within the UK should be able to screen women and offer a FAST MRI scan (and follow up if required) within the specified timeframe (set out in the Trial Assessment section of the Protocol).

All women who attend for their first mammographic screening at the sites will be invited to be screened for eligibility for the study. The participant information will be reviewed by our PPIE team to ensure it is accessible and easily understood for women of all backgrounds.

6 PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility to undergo a DYAMOND FAST MRI takes place once the screening client's breast density is known. Prior to this, eligibility criteria are minimal and are participant-reported, as screening clients can refer themselves for consent.

6.1 Stage 1 (Breast Density Measurement)

6.1.1 Inclusion criteria

- Aged [49 years + 8 months] ≤ [53 years – 1 day] at time of mammogram (source: NBSS)
- Has had a mammogram via the NHSBSP
- Willing and able to give informed consent to Stage 1

6.1.2 Exclusion criteria

- Has not received a breast mammogram
- Aged [<49 years + 8 months] or ≥ 53 years at time of mammogram (source: NBSS)
- Unwilling or unable to give informed consent to Stage 1.

Participants found to be ineligible due to their age upon verification with NBSS after consent has been received will be withdrawn prior to submission of mammograms for density measurement.

6.2 Stage 2 (FAST MRI DYAMOND scan)

Upon receipt of Breast Density Measurement of participants recruited to Stage 1, participants will be screened for Stage 2.

6.2.1 Inclusion criteria

- First screening mammogram (prevalent round) (source: participant-reported)
- Participants with breast density category B as determined by AI breast density measurement (source: SciCom)
- Received standard NHSBSP "no findings" confirmation letter (source: NBSS)
- No absolute contraindication to breast MRI (source: patient-reported, via completion of Standard Safety Questionnaire)

6.2.2 Exclusion criteria

- Breast density category A, C or D (source: SciCom)
- Known recall after mammogram (source: NBSS)
- Pregnant or breastfeeding
- Contraindication to MRI
- Contraindication to gadolinium-containing contrast agents (GDCA).
- Unwilling to have FAST MRI
- Unwilling to allow follow-up of outcomes through data-linkage
- Unwilling to have mammograms measured for density
- eGFR equal to or below 30
- BMI, weight and abdominal girth restrictions may apply to recruiting sites' MRI scanner(s) that could exclude otherwise eligible participants from having the study intervention

Participants found to have conditional contraindications to MRI will be reviewed by the local Radiology service and advice given as to the actions required to facilitate an MRI to take place, in line with local guidelines and best practice.

For example (but not limited to):

- participants who wear a continuous glucose monitor will be asked to remove the device for the scan appointment, or appointment scheduled for a time when sensor is due to be changed
- participants with a coil (Intra Uterine Contraceptive Device) will be asked to confirm the type to ensure it is not an absolute contraindication.

If it is not possible to reasonably adjust for the situation in question, by following local policy, the referral to FAST MRI will be rejected and the participant will not be eligible for a FAST MRI.

7 TRIAL PROCEDURES

7.1 Recruitment and Informed Consent

For a participant to be considered **recruited** to FAST MRI DYAMOND:

1. Consent to Stage 1 – (Screening activity) Consent is received from screening clients to enable research team to complete screening procedures (mammographic breast density measurement and review of breast screening records)
2. Full screening, eligibility assessment and approach for Stage 2 participation
3. Consent to Stage 2 – Consent is received, and FAST MRI is booked
4. FAST MRI is undertaken
5. Participant is **recruited**

7.1.1 Participant identification

Participants will be identified for screening by their usual care team, initially by mammographers during a breast screening appointment who will give screening clients a Stage 1 information leaflet after the mammogram has been performed.

Advertising for the DYAMOND study will also be present in screening clinic waiting areas in the form of posters or postcards. An information video will be available on the FAST MRI Website, with links (or QR code) available on all advertising materials and study updates including calls to recruitment will be shared via Social Media (including but not limited to Facebook and X.

Participants may also be identified by the local NHS research team who will contact screening clients to check if they received the study information unless the client has already consented to Stage 1, or have already declined.

Participants consenting to Stage 1 will be consenting to having their breast screening records looked at by the local research team to assess them for eligibility for participation in the FAST MRI (Stage 2). Following a "cooling off period" of 10 working days from receipt of information about the study, the mammograms of those who have given consent to have their mammographic density measured will be sent via Image Exchange Portal (IEP), utilising pseudonymisation, dedicated research node, and cloud storage (where mammographic density measurements will be undertaken). The "cooling off period" allows 10 working day for consenting screening clients to change their minds and withdraw consent to be screened for eligibility (as is common in qualitative studies).

7.1.2 Screening and eligibility to receive a FAST MRI

- The research team will review the breast screening record (NBSS) of potential participants consenting to Stage 1 to check if the mammogram has been reported by the screening service and are aged [49 years + 8 months] ≤ [53 years – 1 day]. Interrogation of NBSS will be facilitated by bespoke software (created by SciCom).
- Mammograms of participants who have consented to Stage 1 and whose consent has been accepted by the local research team will be measured for mammographic breast density, using an automated tool developed by SciCom and results relayed to the research teams.

- Participants with breast density A, C and D will be contacted by the study teams to notify they are not eligible to have a FAST MRI.
- Participants with breast density category B(26) will be identified by the study team.
- Participants who have been recalled by the standard mammographic screening process for further investigations but are otherwise eligible will be notified that they are not eligible to have a FAST MRI, but are still eligible for data linkage. Participants who are ineligible for any other reason will be contacted and the reason for ineligibility will be explained.
- Participants who remain potentially eligible will be identified and sent the Stage 2 study information. The remaining inclusion and exclusion criteria will be confirmed with the participant during the Stage 2 Informed Consent procedure.
- Eligible participants will be offered participation in Stage 2, and consented individuals will be booked for a FAST MRI appointment.

7.1.3 Payment

No payment will be made to participants, but reasonable out of pocket expenses for participants will be covered for participants attending the FAST MRI scan.

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes informed consent of participants. The PI will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are not standard routine care at the participating site.

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment. Participants will be provided with a contact point where they may obtain further information about the trial. Data and samples collected up to the point of withdrawal will remain in the study, but no further information will be received. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

Should a potential participant require an interpreter and/or written documents translated into their preferred language, this will be offered, using Trust-approved providers (for example, but not limited to, DA Languages or LanguageLine).

Participant information and consent forms will be available in paper copies for anyone without access to devices and / or internet to ensure no one is disadvantaged due to access to technology.

7.2.1 Stage 1 Consent procedures

Consent to Stage 1 (consent to be screened for eligibility) can be self-directed by the screening client after receipt of the Stage 1 information at their mammogram appointment. Clients who wish to consent to Stage 1 without discussing with a member of the research team can complete a consent form (paper or electronic version by following a link or QR code) and submit to the research team.

Clients who do not wish to be contacted regarding Stage 1 will have the opportunity to complete a brief form (paper or online) to notify study teams of their decision.

Clients who have not completed a Stage 1 Consent Form or a decline form will be identified by the study teams and contacted (by phone, text, email, or post) to check whether they received the study information, to answer any questions, and to offer them participation in the study. If willing, informed consent will be received (electronically or by paper).

7.2.2 Stage 2 Consent procedures

Those participants who are deemed potentially eligible at Stage 2 screening (those not recalled/normal or no-findings, of age [49y+ 8m ≤ 53y -1d] and with B-density breasts) will be sent study information for Stage 2 (usually by post, or by email or text if preferred by participant).

10 working days later the research team will contact these potential participants to discuss the opportunity for them to take part in Stage 2 (to have a FAST MRI). The research team will confirm the women have understood the Stage 2 participant information and will complete or confirm the remaining eligibility criteria questions with the participant.

The informed consent conversation should include:

- The nature and objectives of the research study
- MRI Safety Checklist
- Review of the written material (participant information sheet and consent form)
- An overview of FAST MRI
- Possible risks associated with their participation.
- The opportunity for potential participants to ask questions.

The process of what would happen if there were a positive result from the FAST MRI (MRI 3b, 4 or 5) is also explained during this contact. The research nurse will explain that positive results would be delivered by telephone and would necessitate further investigations at the participant's local breast screening service's assessment clinic and the individual's GP will be notified. Explanations are also given about the two types of negative results, including that both types of negative result from FAST MRI would be delivered by letter. These include the "normal" results letter for MRI 1&2 and the "early call back" results letter for MRI 3a. Participants are given time to consider being part of the study and to ask questions prior to informed consent being obtained.

Should the researcher have any concern about whether the potential participant does not have capacity or full understanding of the study, the researcher should not progress the consent until they have had further discussion with the PI.

If the inclusion criteria are met and remote consent is received, baseline data are obtained remotely (including clinical and particularly breast history, risk factors for developing breast cancer, menopause status and information on protected characteristics).

Where remote consent is not possible, the researcher will gain verbal consent to gather baseline data and to book the FAST MRI scan, and participants will be supported to provide their written consent prior to the FAST MRI procedure.

An appointment to have a FAST MRI is arranged and booked at a time convenient to the participant. Those who are pre-menopausal and having a regular menstrual cycle will be booked between day 6 and16 of their cycle).

Booking confirmation is sent by post.

The participant then attends the appointment for FAST MRI scan, where the MRI Safety Checklist is confirmed and signed by the participant, written study consent is received (if it had not been possible prior) and a FAST MRI scan is undertaken.

7.2.3 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies.

Central pathology collation of cancers detected for future translational research: the cancers detected by FAST MRI during this study will be centrally reviewed by an expert histopathologist as follows:

- Histological review
- Molecular categorisation
- Four field assessment of the microenvironment for Tumour Infiltrating Lymphocytes (TILs)

Participants will be identified by the research team regarding participation in the biological sample study.

A separate Participant Information Sheet and Consent Form will be offered to those recalled for further investigations from their FAST MRI scan. Participants will be approached for consent for a sample to be sent to the University of Birmingham (UoB) for additional analysis and potential donation to the UoB tissue bank either by their clinical team or a member of the research team.

The Research Nurse will ensure that the consenting process is appropriately delegated.

7.3 Randomisation

All those who participate in the FAST MRI DYAMOND study will receive the FAST MRI scan. There will be no randomisation.

7.4 Blinding

No blinding will take place in this study.

7.5 Data collection

7.5.1 Demographics and baseline clinical data

We will collect demographic information, including about protected characteristics, for all participants at the time of the Stage 2 remote consent process. At this time, the research team will also obtain baseline data from the participant about clinical and particularly breast history, risk factors for developing breast cancer and menopause status.

7.5.2 Participant-reported outcomes

Participants will be asked to complete a FAST MRI survey about their experience. A purposive selection from survey responses and participant demographics will be used to identify and interview up to 60 participants (from across sites), to gain greater understanding of the impact of the research process and acceptability of FAST MRI.

7.5.3 Clinical assessment and outcomes of FAST MRI findings

If a participant's FAST MRI is classified as:

- MRI 1 or 2 (17), the participant and GP will be sent a normal findings confirmation letter by email (or by post if no access to the internet).
- MRI 3 (17), the scan will be additionally arbitrated by an expert panel of FAST MRI readers. They will decide whether the scan should be reported as MRI 3a or MRI 3b.
    - MRI 3a classification scan: the participant and GP will be sent a letter by email (or by post if no access to the internet) telling them that they will be invited for a repeat FAST MRI in 1 year. Then in 1 year the research team contact the participant to arrange a Y1 FAST MRI at convenient time (within day 6-16 of their menstrual cycle if having a regular menstrual cycle).
    - MRI 3b classification scans will follow the same pathway as MRI 4 or 5 classifications.
- MRI 3b, 4 or 5 (17) the research team contact them and their GP by telephone to let the participant know an appointment has been made for them to attend a local screening assessment clinic for further investigation with "triple assessment" and biopsy with localisation clip placement (under ultrasound, stereotactic, tomosynthesis or MRI guidance). Additionally, they will explain the opportunities these participants will have to have central pathology cancer collation, review, analysis and for tissue donation and will send the relevant information to these participants ahead of their appointment.

If MRI 3b, 4 or 5 on the initial Y0 FAST MRI but no cancer confirmed at biopsy (histology), both the participant and their GP are informed that they will be invited for a repeat FAST MRI in 1 year. Then in 1 year the research team contact the participant to arrange the FAST MRI at a time convenient to them (within day 6-16 of their menstrual cycle if having a regular cycle).

At Year 1 scans will be classified into MRI 1/2 (no further action required) or MRI 4/5 with a referral to the assessment clinic. Readers at Y1 will have access to the Y0 scans for reference.

For all participants with MRI 3b, 4 or 5 at Y0 and for all those with MRI 4 or 5 at Y1, biopsy and localisation clip placement should be performed by the local direct care breast screening team who should use their discretion for choice of imaging modality to guide the biopsy. If the area of concern identified on the FAST MRI scan is not visible on conventional imaging (ultrasound, mammography or digital breast tomosynthesis) then an MRI-guided biopsy and localisation clip placement should be arranged and attempted as per local practice.

Those found to have cancer will be treated as per local practice appropriate for the size, stage and type of cancer detected. In addition, there will be central pathology cancer collation.

MDT recommendations for participants with MRI 3b, 4 or 5 should be followed, in accordance with best standard and local practice. This could include, for example, recommendations for a repeat breast biopsy or biopsies or for further tests such as a full protocol breast MRI if required. Recommendations will be made entirely by clinical need. Participants will be cared for by the clinical care team and will have opportunity to discuss their care with local clinicians, including the potential risks and benefits of each procedure.

Data on MDT discussions and outcomes for all participants with MRI 3b, 4 or 5 will be collected. They will remain a study participant until the end of trial, provided ongoing consent is maintained.

Cancer registry and NBSS records will be reviewed during the study to confirm screen-detected cancer data for all women taking part in the study including the data link participants. The data link participants are those women with BI-RADS B mammographic density who consented to be screened

for eligibility but did not have a FAST MRI scan for any reason and have not opted out of data linkage. This review will help to identify any interval cancers that occur during the study for these women and for study participants.

A follow-on funding application will be submitted to review the interval cancers for study participants beyond the end of the study.

7.6 Trial assessments

7.6.1 Trial assessment monitoring

More than 98% of activities with an asterisk (*) should be completed within the timescale outlined below.

Sites falling between 95-99% should consider an internal review of current process and more frequent audit checks.

Any site falling below 95% should inform the Central Study team for advice using the CAPA (Corrective and Preventative Action) framework.

Trial assessment schedule			
Day	Name of activity	Activity	
		Research team	Screening client
0	Routine mammogram appointment	Stage 1 Participant Information Leaflet and Consent form given	Screening client completes consent to be contacted form within 4 weeks of the mammogram
Within 5 working days of mammogram	Second contact with Stage 1 Participant Information Leaflet	Stage 1 Participant Information Leaflet sent to any eligible screening clients who have not already consented or declined	
10 working days	Cooling off period	No research activity to be undertaken to give women a chance to withdraw consent	
2 weeks from mammogram appointment	Reminder notification	Local research team send out text reminder to any remaining clients who have not consented or declined	
	Age verification	Local research team review age of participants (via NBSS) and either accept their consent (if eligible) or decline it. Participants not eligible based on age will be notified.	
Within 25 working days from mammogram appointment	SMART Portal entry*	Screening client is registered on the SMART Portal ready for IEP transfer of mammogram	
Within 25 working days from mammogram appointment	Mammogram density reported*	Mammogram sent via IEP to a dedicated research node for density measurement	

Within 6 weeks from mammogram appointment	NBSS report*	Report run by research team for women with BI-RADS B density to identify those who have been sent a normal results (no findings) letter	
Within 7 weeks from mammogram appointment	Follow up phone call*	Research nurse contacts the potentially eligible screening client (consent to be contacted, breast density B and not recalled from standard screening mammogram sent a standard NHSBSP "no findings" letter) to discuss participation. Informed consent received. Baseline case report form (CRF) completed e.g. Tyrer-Cuzick Risk Calculator for Breast Cancer Risk Assessment. FAST MRI appointment booked (day 6-16 of menstrual cycle if applicable). FAST MRI appointment letter sent in post.	
Within 16 weeks from mammogram appointment	FAST MRI scan* (Day 6-16 of menstrual cycle if having regular periods)	Standard care MRI safety questionnaire completed. FAST MRI scan undertaken	
Within 17 weeks from mammogram appointment	FAST MRI scan transfer*	FAST MRI scan sent via IEP to the dedicated research node	
Within 22 weeks from mammogram appointment	Results*	Letters sent to women with MRI 1, 2 & 3 to inform no findings (MRI 1&2) or early call y1 (MRI 3a)	
Within 22 weeks from mammogram appointment	Phone call (MRI 3b, 4&5) *) *	Local team call women with MRI 3b, 4 and 5 and contact the GP. Information about central histology collation and tissue donation explained and then sent out to these participants	
Within 22 weeks from mammogram appointment	Invitation to donate biopsy sample sent	Copy of Participant Information Sheet for additional tissue and Consent Form sent to participant AFTER the clinical invitation to assessment clinic has been sent. The PIS and Consent Form should be sent no later than 1 week before the appointment (if via email) or 10 days if via post.	
Within 25 weeks from mammogram appointment	Assessment clinic attendance for participants with MRI 3b, 4 and 5	Women with MRI 3b, 4 & 5 seen at local screening assessment clinic for triple assessment, biopsy and localisation clip. Support given by screening/research nurse at assessment clinic appointment and (optional) consent for tissue donation requested.	
Within 26 weeks from mammogram appointment	Sample storage (cancers only)	Biopsy tissue sample sent to North Bristol NHS Trust for immediate storage (if consent was given)	
FAST MRI repeat (1 year post scan) For all participants with MRI 3a at Y0 and those with MRI 3b, 4 or 5 at Y0, but no cancer confirmed at biopsy (histology)			

8 weeks prior to FAST MRI scan anniversary	Follow up phone call*	Research nurse contacts the screening client to book in second FAST MRI scan. Details of previous medical history over the past year (re)confirmed, consent reconfirmed and second FAST MRI scan booked (between day 6-16 of menstrual cycle if having regular periods)	
Day 6-16 of menstrual cycle if premenopausal	**FAST MRI scan 2***	**All participants with MR3a at Y0 and those with MRI 3b, 4 or 5 at Y0 but no cancer confirmed at biopsy (histology)** Standard care MRI consent and safety questionnaire completed. FAST MRI scan undertaken and images sent via IEP to dedicated research node	
Within 1 week from FAST MRI scan 2	FAST MRI scan transfer*	FAST MRI scan sent via IEP to the dedicated research node	
Within 6 weeks from FAST MRI Scan 2	Normal screening letter sent to women with MRI1&2*	Letters sent to women with MRI 1 & 2 to inform no findings (MRI 3 is not an option for FAST MRI readers at Y1)	
Within 6 weeks from FAST MRI Scan 2	Phone call (MRI 3b,4&5) *	Research team call women with MRI 3b, 4 and 5 and contact the GP	
Within 6 weeks from FAST MRI scan 2	Invitation to donate biopsy sample sent	Copy of Participant Information Sheet for additional tissue and Consent Form sent to participant AFTER the clinical invitation to assessment clinic has been sent. The PIS and Consent Form should be sent no later than 1 week before the appointment (if via email) or 10 days if via post.	
Within 9 weeks from FAST MRI Scan 2	Assessment Clinic for women with MRI 4 and 5	Women with MRI 4&5 seen at local breast screening assessment clinic for triple assessment, biopsy and localisation clip	
9 months before study end	Sample storage (cancers only)	Biopsy tissue sample sent to North Bristol NHS Trust for immediate storage (if consent was given) – once request received by study team from central research team	
All women			
End of study		Final review of cancer registries and NBSS	

7.6.2 FAST MRI imaging

The FAST MRI scan should be carried out within 10 weeks from the screening mammogram. Women should be offered the next available scan date. If it is not possible to book a scan within 10 weeks from the mammogram due to scanner capacity then the next possible scan date should be offered but the

Central Research Team should be notified as soon as possible, with the above (7.6.1) monitoring procedure followed.

7.6.3 Management of abnormalities from FAST MRI scan

Any abnormalities identified through the reading of the FAST MRI scan should be fed back to the clinical team as well as the FAST MRI Research team. The results for MRI 3b, 4 and 5 should follow the clinical pathway for screening assessment clinic referrals.

7.6.4 Arbitration for MRI 3 FAST MRI scan result

Individuals who have an MRI 3 result from their FAST MRI scan should be reviewed by three members of an expert panel. The panel should decide whether the participant requires further assessment = MRI 3b (as above pathway for MRI 4 and 5) or if a follow-up FAST MRI scan after 1 year is appropriate = MRI 3a.

7.6.5 Future training and machine learning

The anonymised image data comprising the mammogram and FAST MRI images (with known outcomes) will be collected for future training of FAST MRI readers and machine learning algorithm development. NBT will be the Data Controller for this study and will have oversight of how the data is shared within training and development.

8. QUALITATIVE EMBEDDED SUB-STUDY

Following their first FAST MRI scan, participants of the QA and FAST MRI (Stage 2) study will be sent a survey to gauge the acceptability of the intervention. A subset of participants (up to 60 women) will be invited to have an interview about their experience as part of the embedded qualitative research on intervention acceptability. Participants in the Qualitative Assurance phase will also be asked to complete the FAST MRI Survey. Participants at the host site will be asked to take part in an interview to obtain feedback on the FAST MRI appointment.

8.1 Embedded qualitative assessment of the acceptability of the intervention

After a participant's FAST MRI scan, they will be asked to complete the FAST MRI survey to collect feedback about the FAST MRI appointment. The survey will also give the participant the option to agree to be contacted to take part in an interview to discuss their results further. If the participant has not completed the questionnaire but not informed the staff member that they do not wish to complete the questionnaire, they may be sent a copy by email or called to complete the questionnaire.

We will collect demographic information, including about protected characteristics, for all participants at the time of the remote consent process. This information along with results of the analysis of the survey will be used to purposively select potential participants for the qualitative interviews. The aim of these is to assess the equality and equity impact of the research and will influence study design for the future RCT. If disproportionate disadvantage is found for any group for the current study, we will adapt the study design of the RCT to minimise this selection bias. If this is identified whilst this study is ongoing, amendments to process will be investigated, and discussed with the TSC and the PPIE advisors. If deemed feasible they may be rolled out following obtaining appropriate approvals.

Each participant will be asked for feedback on acceptability relating to FAST MRI via a survey. This will be informed by the Theoretical Domain Framework (TDF) (53,54)]. Interviews with up to 60 women will be undertaken. The aim is to gain greater understanding of the impact of the research process and the acceptability of the FAST MRI. A priori framework analysis using the TDF will be undertaken.

8.2 Qualitative analysis

Ritchie and Spencer (1994) outline four types of research questions that framework analysis can helpfully address:

- Contextual: identifying the form and nature of what exists
- Diagnostic: examining the reasons for, or causes of, what exists
- Evaluative: appraising the effectiveness of what exists
- Strategic: identifying new theories, policies, plans or actions

If an inductive approach to data analysis is undertaken, themes are generated from the data through open (unrestricted) coding, followed by refinement of themes. If the approach is deductive, the themes and codes are pre-selected based on previous literature, previous theories or the specifics of the research question (55).

However, as is the case with the current research, in many cases, a combined approach is appropriate when the project has some specific issues to explore, but also aims to leave space to discover other unexpected aspects of the participants' experience or the way they assign meaning to phenomena.

The Framework Method can support this hybrid approach being adapted for use with a combination of deductive and inductive qualitative analysis, in this case using an a priori implementation framework whilst remaining open to the possibility that the framework is not complete or completely implementable within an acute NHS trust (56,57). Following transcription of the interviews (the auto-transcription from teams is not sufficiently accurate to be of use, therefore the researcher will

undertake smooth transcription from the MP3), transcripts will be uploaded to NVivo 12 (58), and then the Gale et al (2013) framework analysis process will be undertaken:

Stage 1: Transcription

Stage 2: Familiarisation with the interview

This will be undertaken by relistening to the interviews and reading and rereading of the transcription and making notes of initial thoughts.

Stage 3: Coding

Integrating initial thoughts, the researcher looks for diversity and similarity in the transcripts, to start to make meaning from the dataset, and apply labels to specific segments of transcript/data.

Stage 4: Development or selection of a working analytical framework

Initially patterns of meaning are considered using the codes collated in stage 3, and then reflecting on implementation science theory and a range of frameworks. This is facilitated by using NVivo, and the use of a code book.

Stage 5: Applying the analytical framework with consideration of additional inductive codes

Coding patterns are considered in light of the a priori framework with tentative themes being redefined or discarded.

Stage 6: Charting data into the framework matrix

Refined codes are then charted against the a priori framework, and additional themes are retained for inductive inclusion in the interpretation of the data.

Stage 7: Interpreting the data

Following stage 6, the researcher reflects the a priori framework and additional inductive themes back to the scoping review, additional literature considering leadership, implementation and the context in which the research was undertaken (56,59).

9. FAST MRI READER EMBEDDED SUB-STUDY

FAST MRI Readers are both researchers and study participants.

We will report FAST MRI reader outcome data (by professional group, experience and demographics data), diagnostic accuracy of readers (individually and by reader group and NHS site), numbers of scans requiring arbitration, standard arbitration outcomes and expert panel arbitration outcomes.

9.1 Inclusion / Exclusion Criteria:

Readers must be:

- Employed by a participating site
- A mammogram reader for NHSBSP
- Have completed FAST MRI DYAMOND Reader Training, or a subset of this training termed Refresher Training*
- Credentialled (reading and reporting on scans with known outcome, achieving a pre-defined specificity and sensitivity (60))
- Able to provide their Informed Consent

In addition, to become a certified FAST MRI DYAMOND Reader and begin reading DYAMOND participant scans, the Reader must also be ICH GCP trained, have submitted a Research Curriculum Vitae, and be signed off as a Reader/ Researcher by the local PI.

*Training for readers who have previously undertaken FAST MRI interpretation training and credentialled may be in a condensed format comprising refresher training presentations plus reading and reporting a smaller subset of scans with known outcome.

Baseline information (demographics, qualifications, credentialling results etc.) will be collected by the Central Study Team when Informed Consent is received.

9.2. Reader Consent procedures

Potential FAST MRI DYAMOND Readers will be identified by the local PI or by the Central Study Team if the Reader has previously undergone training under the FAST MRI Programme. The Reader Participant Information sheet will be sent to potential participants, who will be given as much time as they need to consider their participation and have opportunity to ask questions and be supported in their decision making by their local PI or by the Central Research Team. Consent to become a FAST MRI DYAMOND Reader will be facilitated via OnlineSurvey. A member of the Central Research Team will register the NHS email address of interested Readers and send the Reader a password-protected link to the consent form. Submission of that form to the Trial Manager will confirm the Reader's consent to participation in the study.

Readers wishing to consent will receive a copy of their completed consent form, electronically from a Central Research Team representative.

A further copy of the consent form will be retained by the Central Study Team in line with GCP and data protection principles.

The site PI will be notified when a Reader has fully certified and is therefore able to be signed off as a FAST MRI DYAMOND Reader on the local delegation log. Results of applicants who do not meet

specificity and sensitivity criteria will not be relayed to the site PI by the Central Research Team, although the applicant is free to disclose this information directly if they wish.

9.3 Continuing Professional Development (CPD)

Training for this study has been granted continued medical education (CME) accreditation in accordance with the continued professional development (CPD) scheme of the Royal College of Radiologists.

9.4 Baseline Reader data

Following receipt of Reader Informed Consent, demographics data will be collected from the Reader. This information will include:

- Initials
- Name
- Contact details
- Site location and job role
- Reader experience

9.5 Reader scores

Potential Readers will complete training and read example scans (standardised assessment dataset) under their pseudonymised user login. Their interpretations will be compared with the true outcome of each scan and each potential reader's diagnostic accuracy performance will be scored by the study Statistician. The Reader scores (Specificity and Sensitivity) will remain confidential, with only restricted members of the Central Research Team and the Reader in question being in receipt of the scores.

9.6 Participant scan reading

Readers who have completed DYAMOND credentialling and who have become certified DYAMOND Readers and signed off by their PI as a delegated Reader will be allocated participant scans.

Once readers have been fully certified as a FAST MRI: DYAMOND reader, they will be able to read scans from the main DYAMOND study.

Access will be granted to the scans awaiting reading via RiViewer (by SciCom of RSNFT) where the anonymised scans and clinical supporting information will be displayed. For each interpretation session readers will need to login to the dataset with their unique Study Identifier and password.

Readers will perform scan interpretation alone and keep their answers and opinions confidential.

Readers can stop and start reading sessions at any time. Most readers have told us that batches of around 50 cases have worked well for them, though at certain stages of the study, there may be fewer images available to review.

All FAST MRI: DYAMOND scans will be read by two certified readers, and if required, arbitration by a third certified reader and/or expert panel arbitration will take place.

9.7 Withdrawals from the Reader sub study

The Reader Participant will remain free to withdraw at any time from the trial without giving reasons and without prejudice. Participants can relay their decision to a member of the Central Research Team and their PI. Data about the Reader, and results scan reading collected up to the point of withdrawal will remain in the study, but no further information will be obtained.

10. WITHDRAWAL CRITERIA

Participants may withdraw from the study at any point without penalty. Should a participant request to withdraw from the study, they will be asked for consent to follow up their data until the end of the study.

If a participant no longer fits the eligibility for FAST MRI scan or withdraws from the study before the scan has been undertaken, the PI will continue to follow up the participant electronically (via screening data and the cancer registry) until the end of the study unless the participant asks them not to do this (opt out as consent given for this in the consent to be screened for eligibility form).

Should a participant who has been withdrawn, request that no further data is collected, then only the data gathered previously will be held and included in the study. Where possible a reason for withdrawal should be collected and documented on the Study Withdrawal Form.

Participants who have withdrawn from the study before the FAST MRI scan should not need to be replaced as the study design takes into account a 4% drop out, but regular communication with the statistician should take place.

11. COLLECTION, STORAGE AND ANALYSIS OF CLINICAL SAMPLES

Participants who have a biopsy within the study will be asked to donate a sample for analysis and future research if it is shown histologically to be a cancer.

11.1 Sample collection

The research team will notify the clinicians (including the breast screening nurse) before the assessment clinic that the participant has discussed the option of additional tissue analysis and donation and the process of collecting this sample.

The research team will ensure that all appropriate equipment for the additional FAST MRI research sample is provided for participants who have consented to biological sampling and ensure that the sample is correctly labelled with the study name, participant ID and date of sample collection. It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

11.2 Sample storage

Once the sample has been provided, the research team should store the sample appropriately and notify the Central Research team that there is a sample pending collection. Samples will be sent to and stored at to North Bristol NHS Trust and held at room temperature storage within the Trust's pathology department under their Standard Operating Policy. They will be link-anonymised by a member of the central research team and stored until the end of the biopsy period (around February 2026).

A copy of the local histology report will be sent to the Central Research team electronically once it becomes available. The histology report will be linked by the study name, participant ID and date of collection and personal identifiable information removed.

11.3 Sample analysis

Once the biopsy period has completed, NBT will send the batch of samples that are biopsy-proven cancer and the histology reports to the University of Birmingham Human Biomaterials Resources Centre (HBRC) via HBRC-arranged courier for analysis and long-term storage. The HBRC hold an up-to-date Human Tissue Authority License. Should additional funding become available during the study, further analysis will be undertaken to profile the microenvironment.

11.4 Withdrawal from the sample sub study

Should a participant wish to withdraw from the ancillary research, they (if they wish) can continue to take part in the main diagnostic yield part of the study. This will be stated on the Consent Form and a notification should be sent to SciCom and Warwick Clinical Trials Unit.

11.5 End of analysis storage

After all study analysis has been undertaken, if the participant has consented, then the samples will be gifted to the HBRC for future research.

12. DEFINITION OF THE END OF TRIAL

The end of trial is defined as when;

- all first (Year 0) FAST MRI scans have been completed,
- all second (Year 1) FAST MRI scans have been completed (for the subset of women who require one),
- and when the final review of the National Breast Screening Service (NBSS) databases, Breast Screen Select and Cancer Registry has been completed.

13 TRIAL TREATMENTS

Name and description of each Non-Investigational Medicinal Product (NIMP):

For a FAST MRI (contrast-enhanced, abbreviated breast MRI scan) to be performed, a contrast agent is needed. The brand of agent may depend on local preference at each site, but the agents will be those used within each site's standard clinical care and therefore all risk and protocols will be followed in line with Trust guidance. The dose of gadolinium contrast agent will be standardised for all patients at each site.

14 PHARMACOVIGILANCE

14.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

14.2 Recording and reporting of SAEs, SARs AND SUSARs

The period over which these AEs, ARs, SAEs, SARs and SUSARs must be recorded and reported as follows.

Type of reaction	Active monitoring period
For AEs	Consent-End of study
SAEs	Consent-End of study
ARs	1st contrast dose < End of study
SARs	1st contrast dose < End of study
SUSAR	1st contrast dose < End of study

If a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes.

All SAEs should be reported to the Sponsor. Assessment of seriousness, causality and expectedness for trials involving the contrast agent must be made by the sponsor or designated authority e.g., CI. If an authorised doctor from the reporting site is unavailable, initial reports without assessment of whether the event was anticipated should be submitted to the Sponsor by a healthcare professional within 24hours of becoming aware of the SAE but must be followed-up by medical assessment as soon as possible thereafter.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to NIMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder (if not the sponsor) of SUSARs within the required expedited reporting timescales.

14.3 Responsibilities

14.3.1 Principal Investigator (PI)

Checking for AEs and ARs

1. Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

14.3.2 Chief Investigator (CI) and Lead Co-Applicant

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.

2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated.
3. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

14.3.3 Sponsor

1. Central data collection and verification of AEs, ARs, SAEs and SARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

14.4 Notification of deaths

Only deaths that are assessed to be caused by the contrast agent (NIMP) will be reported to the sponsor. This report will be immediate.

14.5 Pregnancy reporting

Whilst it is unlikely that any participants become pregnant during the study, due to the age of the cohort, should a participant report a pregnancy before the FAST MRI scan, they should be withdrawn from the study (as per the withdrawal procedure).

If a participant reports a pregnancy after the FAST MRI scan, and they may have been pregnant at the time of the scan, information should be passed on to the participant's midwife. Data follow-up will continue unless requested otherwise.

15 STATISTICS AND DATA ANALYSIS

A Statistical Analysis Plan (SAP) will be developed to provide full details of the planned analysis.

15.1 Sample size calculation

From previous studies, in population-risk women of all mammographic densities, the number of cancers detected by mammogram is approximately 8 cancers per 1000 women screened (61). More specifically, for women aged 50-54 years, having their first screening mammogram (prevalent round), standard mammography finds approximately 7.5 cancers per 1000 women screened (61) (there are no reported figures specific to age 50-52). The addition of MRI may detect an additional 16.5 per 1000 women screened(28) (referenced study conducted in women with mammographically dense breasts (density category D(26)) with DCE-MRI as intervention). Meta-analyses have shown that sensitivities and specificities for FAST MRI did not differ significantly from those for DCE-MRI(14,18) but confidence in the evidence was low and FAST MRI may not pick up as many cancers as DCE-MRI. However, it is expected to be more cost effective than MRI, as it is quicker to undertake and interpret. It is expected to detect more aggressive cancers than mammography and thereby to reduce the numbers of cancers that would otherwise be first detected at a late stage, as missed on mammography.

There is insufficient evidence for the average density group (Bs) as to whether the addition of FAST MRI will be of sufficient benefit to warrant further investigation of this group in a phase III trial. This group, which makes up 40% of the screened population, are excluded from other supplemental screening trials despite a knowledge gap about whether supplemental screening could benefit them. Thus, it was considered necessary to conduct a diagnostic yield study to determine the cancers detected by FAST MRI but missed by mammography in this population.

A Fleming's two-stage design (52) will be used to assess the number of additional cancers detected by FAST MRI. This design allows for early stopping after stage one, which would save patients, funding costs and time continuing to the end of the study if the question could be answered earlier. Based on previous research and consensus from radiologists, health economist and PPI representatives, 4 additional cancers detected per 1000 women screened was deemed the minimum that would be required to be detected to warrant further investigation of this study population in a phase III trial. Setting the lower limit for the cancer detection at 0.004 (4 additional cancers detected per 1000 women screened), the target rate at 0.011, 80% power and a 5% one-sided significance level, then a minimum of 959 women would be required (381 women at the first stage). Thus recruiting 1000 women to the study will allow for 4% dropouts.

The number of participants found to have been recruited based on participant-reported mammogram prevalence, but who are found to have had prior population-risk screening or symptomatic mammogram (verified at close of recruitment via interrogation of Breast Screen Select) will be reported.

An interim analysis will be performed after the first stage and based on these assumptions, the study may be halted for futility if 1 or no additional cancers are detected during the first stage of the study, or if 5 or more additional cancers are detected during the first stage the study may be stopped as greater than the lower limit.

If 7 or fewer additional cancers are detected at end of study, then no further investigation is warranted in this study population. However, if 8 or more additional cancers are detected then it warrants further investigation with inclusion of this study population in a phase III. The additional cancers detected by FAST MRI are likely to be the more aggressive cancers that were missed by mammography (15).

15.2 Planned recruitment rate

A 9-month internal pilot phase after first site opened, and first participant recruited, has been incorporated into the trial to assess the willingness of clinicians and patients to participate. The progression criteria from the internal phase at 9 months are based on site opening, recruitment and compliance with 960 women having a FAST MRI attendance and uses a traffic light system of green for continuing to recruit, amber for considering amending the

trial to improve recruitment either in terms of relaxing the eligibility and/or extending the number of sites and red for considering stopping the trial if there are no possible recovery options.

15.3 Statistical analysis plan

Summary statistics of the patient characteristics will be presented as counts and percentages for categorical variables and means and standard deviations or medians and interquartile ranges for continuous variables depending on the distribution of the data. Comparison of those included in the study with those not joining the study will use chi-squared tests, t-tests or Wilcoxon rank sum test where appropriate.

A flow diagram will be produced showing the number of women at each stage of the recruitment process and analysis, e.g., initially screened, completing consent to be contacted form, number in each breast density category, number with breast density B given all clear, number registered into the study, number having a FAST MRI, number in each MRI classification, number recalled and number having a biopsy (number having each image guidance category of biopsy e.g. ultrasound guided, MRI guided) and number subsequently diagnosed with cancer.

The number of additional cancers detected by FAST MRI for those women with breast density category B recruited into DYAMOND will be assessed and the overall detection rate per 1000 women screened using FAST MRI will be determined as well as the associated 95% confidence interval (CI). The detection of 8 or more cancers would suggest that it is worth considering breast density category B women in a future phase III trial.

The recall rate and biopsy rate together with associated 95% confidence intervals will be determined.

Summary statistics will also be provided for tumour characteristics of the cancers detected (histology, size, grade and stage) and any adverse reactions to the FAST MRI.

This is a single arm study and therefore no formal statistical testing is expected. All women registered into the study will be analysed where possible. Cancer detection rates and adverse events will be analysed using the as treated population that had a FAST MRI. Women who subsequently withdrew consent to participate will be analysed up until the point of withdrawal. To limit missing data, participant's involvement is kept to a minimum with women only expected to attend for a FAST MRI and subsequent investigation depending on the result of the FAST MRI. Data collection is through the screening services and hospital data.

15.4 Interim analysis and criteria for the premature termination of the trial

Using a Fleming's two-stage design, an interim analysis will be performed after the first stage once 381 patients have been recruited, which is anticipated to be around 19 months after grant start. The study may be halted for futility if 1 or no additional cancers are detected during the first stage of the study, or if 5 or more additional cancers are detected during the first stage the study may be stopped as greater than the lower limit for the cancer detection of 0.004 (4 additional cancers detected per 1000 women screened). The results of the interim analysis will be reviewed by the independent DMEC and TSC.

16 DATA MANAGEMENT

Please see Data Management flow charts (Appendices 1 & 2) for further information.

16.1 Image collection and storage

All data that is transferred from the clinical sites to the central image database is fully de-identified and at no point do researchers have access to identifiable information. Further details can be found in the associated Image and Data management protocol.

16.2 Pseudonyms

FASTMRI utilises a Trial ID in the place of Patient IDs. In order to obtain the Trial ID a web portal (SMART Portal) will be utilised to allow sites to submit Trial IDs (See SMART Portal Trial ID Registration section). Secondary pseudonyms are created through a one-way encryption process known as 'hashing' which provides the ability to link the images with the Trial ID and link with other datasets that have generated these pseudonyms in the same manner using the same complex salt.
The pseudonyms are generated during the participant registration process which generates hashed identifiers. This process is undertaken before the images are received from IEP and on the client-side of the SMART portal web form.

16.3 Image collection from NHS sites

Each site is provided with training and guidance documentation to inform the users on the collection processes. Sites are asked for the participating client's identifiers to be registered on the SMART Portal and imaging to be sent to a dedicated Research Node on the Image Exchange Portal. The images and data are de-identified at the point of receipt.

16.4 SMART Portal Trial ID registration

FAST MRI Study sites will register the participants on the SMART Portal in advance of sending the images. This step is required to ensure that the Image collection system is informed of the Trial ID of the participant before the image is received, allowing the image to be identified as belonging to FASTMRI and providing the pseudonym to insert into the DICOM image. The Trial ID uploaded to the SMART portal and the incoming image will be linked through the use of a common secondary pseudonym in the form of a hashed NHS number (see Pseudonyms Section).

Patient identifiers are de-identified at the point of upload. Upon upload, a pseudonym will be assigned to the patient. This will be created by a lossful encoding algorithm and complex salt which will produce an encoded pseudonym that allows the linking of the patient's trial ID with the images.

Each site is issued with a user account for the SMART Portal with an initial password from the Royal Surrey Scientific Computing team. Sites will register a client by entering an NHS/CHI number, a secondary ID, which must be the ID used by radiology (unless radiology uses NHS/CHI), as well as the trial code which uniquely identifies the client.

16.5 Image Collection

FASTMRI collects images using the Image Exchange Portal (IEP). This is advantageous as the processes for transferring images via IEP are well known and robust. FASTMRI has a dedicated node on IEP available for use for receiving images that are to be de-identified. This node is provided by the RSNFT. The node has been set up such that the images are de-identified as they transition from IEP, meaning that no patient identifiable information is received outside the IEP network. A pseudonym is generated using the same technique as described in the section above (Pseudonyms). This results in a common pseudonym between the images and the linking with the FASTMRI Smart portal entry.
Collection sites are requested to submit images through IEP when a new patient is enrolled into FASTMRI. Many sites have internal processes for requesting image transfers via IEP (often through the PACS office). Guidance is provided to utilise these processes where possible. Guidance is also provided showing a step-by-step guide on how to submit images through IEP.

16.6 Data Flow

Images transferred via IEP to the FASTMRI node (hosted at the RSNFT). RSNFT is providing the image collection services for FASTMRI. While the images temporally reside on the RSNFT storage, for added insurance in the case of hardware failure, the system is replicated each evening to a mirror located in a separate building within the Trust. Both the storage and backup systems are also replicated to redundant systems to ensure continuous availability. Regular database dumps of all databases are made every two hours and archived on the backup systems.

16.7 Access to Patient Identifiable Information

Images and data are de-identified at the point they are transferred to FASTMRI. The staff transferring the images via IEP will require access to patient identifiable information. However, these staff will be employees of the collection site. The NHS numbers of the patients whose images are collected are pseudonymised as detailed above. Once the case has been labelled as complete, the lookup is deleted. The case will only be complete once the study is complete.

16.8 Volumetric Breast Density and Background Parenchymal Enhancement on FAST MRI

Automated volumetric breast density measurements and measurements of background parenchymal enhancement will be made by the MRI scanners from the FAST MRI scans whenever possible and comparison made with the outcomes and with the automated mammographic density measurements (from the screening mammograms).

17 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed and agreed by the TMG, TSC, DMEC and CI based on the trial risk assessment which may include on site monitoring. This will be dependent on a documented risk assessment of the trial, the procedures and anticipated frequency for monitoring. Monitoring will be conducted across all sites on a risk proportionate basis, considering enrolment, withdrawal rates, breaches and atypical reported adverse events. This will be considered by the DMEC and presented initially to the TMG and CI.

The monitoring will be conducted by the site, Trial Manager and if necessary, the Sponsor. The processes reviewed may relate to participant enrolment, consent, eligibility, and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. Monitoring can be done by exploring the trial dataset or performing site visits.

Sites may be required to provide a room for the Trial Manager or Sponsor to review documentation or information so that the monitoring can be completed remotely.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the NHS R&D departments before they can be implemented in practice at sites.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File, this can be in electronic format if it is held securely within the NHS site.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required and they will notify the REC of the end of the trial.

If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

18.2 Peer review

The project has been peer reviewed as follows:

- In December 2021, the National Cancer Research Institute (NCRI) Breast Group provided a letter in support of the NIHR's EME application process. Support for funding for our study proposal cited the gradual iterative development of our study proposal with input and support from both the Breast Group and the Translational and Imaging Sub-Group of the NCRI.
- In February 2022, the NIHR Research Design Service (RDS) arranged a formal RDS Review Meeting, including Methodologists, Statisticians and Lay Reviewers, to assess the suitability of our study proposal for funding by the NIHR and the readiness of our funding application for submission.
- In August 2022, the study proposal was awarded funding through the NIHR EME funding stream, researcher-led pathway. This award represents the outcome of review by the NIHR EME Funding Committee and is a national researcher led funding competition.

18.3 Public and Patient Involvement and Engagement (PPIE)

Patient and public involvement is fundamental to this study; public opinion about the acceptability of FAST MRI is important because high attendance for screening investigations is essential to the success of any screening programme. Formal involvement of the public and of women with personal experience of breast MRI has been an important factor in our study design and in understanding that both minimising times spent in an MRI scanner and the absence of ionising radiation in FAST MRI are important factors in optimising the acceptability of the intervention.

We will invite women to contribute to the study PPIE who are underrepresented for breast screening. These are predominantly individuals from the Afro-Caribbean and Southern Asian communities. Representatives will be

engaged via community champions, through outreach work and attending events which already have a high turnout of these communities. Specific FAST MRI workshops in targeted locations will be conducted. We will also work with PPIE members to identify other avenues for public engagement.

The opinion of service users will guide our public facing documents and the development of the information video, along with dissemination of outputs and of potential future FAST MRI studies.

19 REGULATORY COMPLIANCE

The trial will not commence until HRA Approval (including Favourable REC opinion) is received.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

19.1 Protocol compliance

The Sponsor and Chief Investigator will be notified of any protocol deviations. There should be no prospective, planned deviations or waivers to the protocol. Any deviations from the protocol which are found to frequently recur will require immediate action and could potentially be classified as a serious breach.

Protocol deviations should be highlighted at TMG meetings and TSC if necessary, including a discussion on corrective and preventative measures.

19.2 Notification of Serious Breaches to GCP and/or the protocol

The Sponsor and Chief Investigator will be notified immediately of any case where a breach has been identified during the trial conduct phase.

The Sponsor and Chief Investigator will notify the relevant authorities in writing of any serious breach.

19.3 Data protection and patient confidentiality

19.3.1 Data Acquisition

Personal data collected during the trial will be handled and stored in accordance with GDPR and the Data Protection Act 2018.

19.3.2 Data quality monitoring

The quality of the data will be periodically monitored. Each site will be asked to complete regular monitoring and monitoring will be completed by the central research team.

A review of the data (and images) will also be completed by the team using regular reports generated by the SMART portal of patient registration and image/data collection. Statisticians will also review data at interim and full analysis stage of the trial. Feedback will be given to the TMG and TSC and any training or amendments to the protocol will be added as required.

19.3.4 Confidentiality

We have taken steps to minimise any risk to screening client and patient confidentiality. By ensuring that the FAST MRI images are automatically link-anonymised no identifiable participant data will leave the site for analysis.

Online consent (or telephone online consent) will reduce the risk of paper management of Participant Information Sheet and Consent Forms and will be utilised for Stage 1 Consent, Stage 2 Consent and Reader Consent. Paper consent will be utilised for QA participant and Tissue Donation consent. This will

be managed in line with GCP and data protection principles and should be kept in a lockable storage unit, accessible only by delegated members of the research team.

Electronic consent forms will remain on the RSH (Royal Surrey Hospital) / SciCom server, encrypted and protected, for the duration of the study, after which a copy of the entire data file will be sent to the Sponsor site for archiving in line with the Sponsor's archiving policy. RSH will then delete the data from their server.

Contact details of women taking part in the study will be held on the NHS medical notes platforms including NBSS and the research database.

Should there be a breach of confidentiality the Breach protocol should be immediately followed.

19.3.5 Data storage and archiving

Please see Appendix 3 for archiving details. All paper documentation should be held securely at site. Electronic study documentation that contains identifiable participant data should be stored on an NHS Trust drive and the file password protected, with access given to only those within the direct care team or the central research team with specific consent (e.g., monitoring).

19.4 Financial and other competing interests for the chief investigator, co-investigators and PIs at each site

The Chief Investigator, co-lead and other co-investigators declare no conflict of interest. Any potential competing interests which may arise during the study will be reviewed at the Trial Steering Committee and appropriate action or mitigations will be taken under the guidance of the Sponsor.

19.5 Indemnity

A key responsibility of the sponsor is to put in place arrangements for compensating participants if they suffer any harm as a result of their involvement in a project.

The study intervention involves a shorter version of an imaging test that is used every day in NHS Trusts across the UK as part of standard care for many indications including the staging and investigation of breast cancer and also in breast cancer screening for women who are at high risk of developing breast cancer. The safety profile of this study intervention is well documented(48,62).

There is a risk of participant harm from the study through a data confidentiality breach. Care has been taken to minimise this risk by the anonymization of data, and by careful arrangements for the safe storage within NBT of the electronic identifiable data (please see section on confidentiality above). This research is sponsored by NBT, and the NHS Clinical Negligence Scheme applies and provides unlimited cover for NHS staff, medical academic staff with honorary contracts and those conducting research against negligent harm. Non-negligent harm (i.e., harm that has been caused through no fault of those conducting research) is not covered by this scheme and the NHS is unable to agree to pay any compensation for non-negligent harm in advance.

19.6 Amendments

Any need for an amendment will be initially discussed by the TMG and Sponsor, and where required by the TSC.

The Central Research Team will submit a request to Sponsor with the relevant updated documents. Once approved, the team will submit the amendment to the HRA for approval. Each site will receive notification of the

submitted amendment and the assessment from the regulatory body so that an impact assessment can be made at each site.

An amendment log will be kept by the Central Research Team and shared with sites with each new amendment. This will keep track of the newest version of the Protocol and the changes which have been made.

19.7 Post trial care

Following on from the end of the study, participants will be advised to contact their GP should they have any concerns about their health.

19.8 Access to the final trial dataset

Before the publication of the study and data-lock, the statistician, and methodologists (including the Chief Investigator) will have access to the final dataset. The anonymised data may also be seen by the other members of the research team.

Once the primary outcome has been published, on request, the data and FAST MRI images may be shared outside the FAST MRI Programme. This will need to be approved by a minimum of 2 members of the TMG by completing a “FAST MRI data request form” which can be found on the FAST MRI webpage. Ethical approval for the establishment of a research database will be sought.

20 DISSEMINATION

20.1 Dissemination policy

The data is owned by the Sponsor, North Bristol NHS Trust.

20.1.1 Scientific audience

The protocol for the study will be published within a peer reviewed journal and the results of the study presented at National and International meetings on behalf of North Bristol NHS Trust and published within a peer reviewed journal. These publications and presentations will acknowledge the sponsor and funder of the study.

On completion of the trial, the data will be analysed, and tabulated, and final study reports will be sent to the relevant authorities (funder, HRA, NHSBSP RIDAC). The primary outcome paper will be submitted to an Open Access peer reviewed journal.

20.1.2 Public audience

A lay summary will be disseminated to:

1. All involved bodies (e.g., BUST, ICPV)
2. Formal PPIE group
3. FAST MRI mailing list.
4. Uploaded to the FAST MRI website
5. All FAST MRI readers within the study
6. All participants

Social media will also promote these findings through the NBT Research and Innovation teams and the FAST MRI twitter account. Sites who have taken part in the study will also be given the opportunity to disseminate the findings.

20.2 Authorship eligibility guidelines and any intended use of professional writers

Members of the Research team who are eligible for authorship according to the **criteria of The International Committee of Medical Journal Editors** will be a named co-author on publications and any study reports.

21. SITE RESEARCH ACTIVITIES

Individual sites may be opened in phases to allow them to commence Reader certification and Reader activities prior to site's recruitment of study participants (QA Phase, Stage 1 and Stage 2 recruitment) and independent of set-up activities which relate to the provision of the intervention at their own site.

1. Phase 1: CC&C and greenlighting for DYAMOND Reader Activities

   Upon receipt of Phase 1 Greenlight, a site's FAST MRI Readers who are appropriately certified as a DYAMOND Reader can review another site's FAST MRI scans.

   A site is **not** expected to approach or recruit any study participants until they have been issued Phase 2 Greenlight.

2. Phase 2: CC&C and greenlighting for identification, approach and recruitment of study participants to the DYAMOND Study.

   Upon receipt of Phase 2 Greenlight a site can: recruit participants to the *Quality Assurance of FAST MRI Scans* phase of recruitment and subsequently to the main study (*Stage 1* and *Stage 2*). Sites are not expected to conduct any recruitment activities until they have been issued Phase 2 Greenlight.

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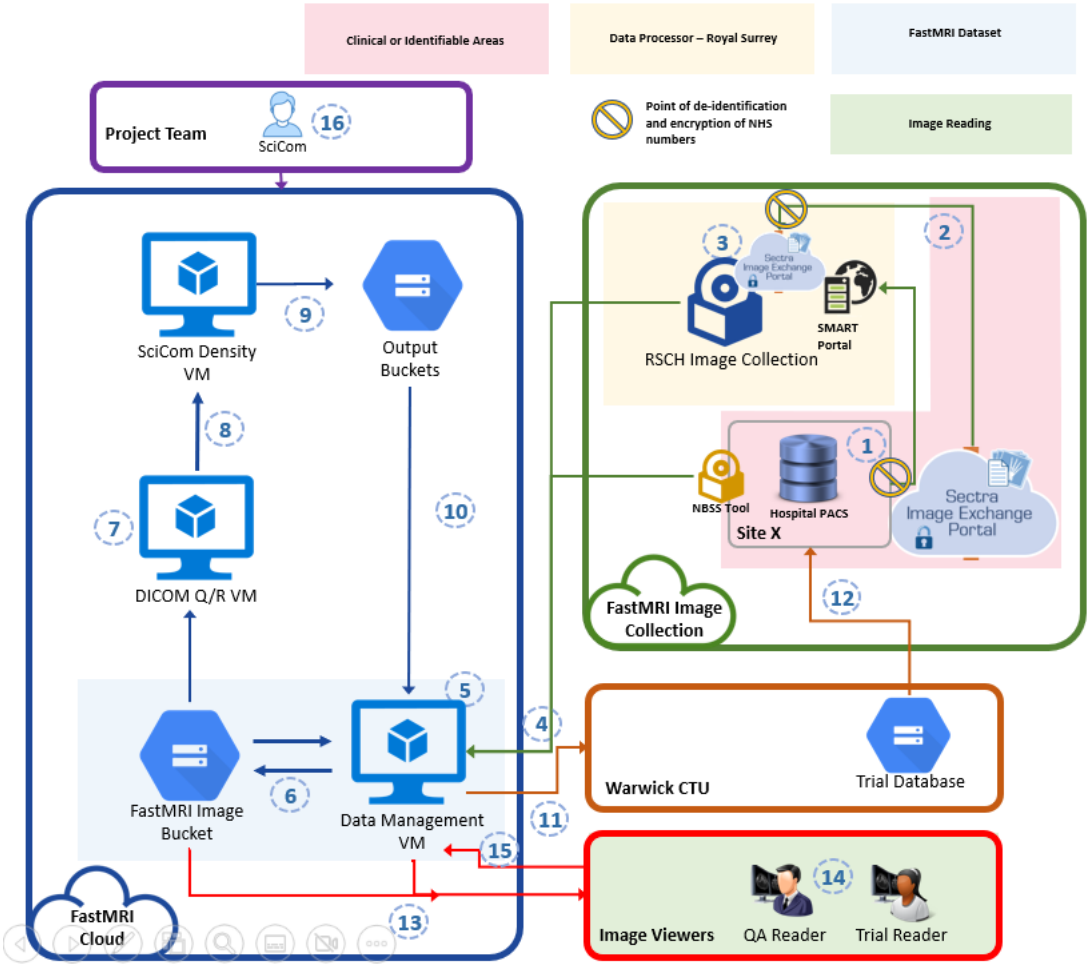
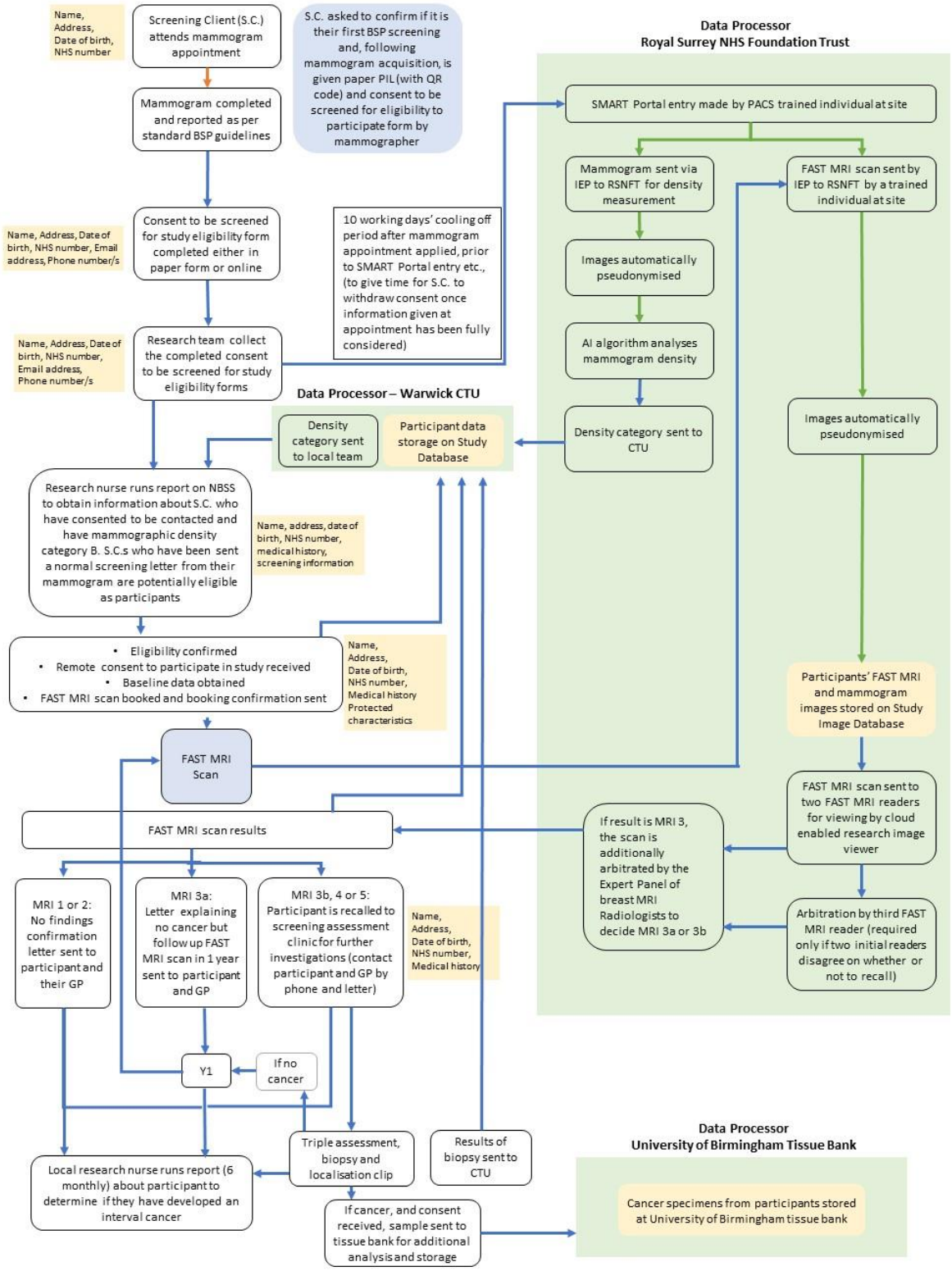
22. APPENDICIES

1. Data Flow diagram



DYAMOND cloud_deployment v1.2

2 Data Logic Flow Diagram



3 Trial documentation and archiving

Archiving is managed by a third-party provider at NBT. At the end of the study a minimum period of six months should be allowed to ensure that all queries are answered, and study related paperwork collected. The documents will be retained for 5 years after the conclusion of the study.

Archiving should take place following this 6-month period but within twelve months of the end of the study. All essential documentation should be checked to ensure the following:
(a) All documentation should be complete and legible
(b) The study file is complete, tidy and documents are stored in a logical order.
(c) All Case Report Forms (CRFs) and other patient-related medical documentation are collated and ensure all data queries are resolved. (d) Documents held in lever-arch files are removed in preparation for archiving to reduce the space required for archiving.
(e) Documents may be held together by plastic archiving clips but all paper clips, elastic bands, staples or metallic means of combining sheets should be removed to prevent rusting or other chemical deterioration.
(f) Documents are indexed in a manner that allows all documents to be always traceable and readily accessible to the authorities upon request.
(g) An NBT Archiving Record Form should be completed, filling out the list of documents to be archived (or attaching a separate list).

Once documents are prepared and ready for archiving, please contact FAST MRI Programme Team for the archiving boxes.
(b) Complete a 'Completing the transmittal/using the barcode label' document, if appropriate.
(c) Contact FAST MRI team to arrange for collection of the archive boxes for transfer to the off-site storage facility.
(d) A copy of the archiving indices, file location identification (third party barcode/ unique identifier) and archive provider must be provided to R&I when the essential documentation is archived.
(e) FAST MRI team will maintain a log of archived projects including their box numbers and locations for retrieval

Currently, there are no guidelines relating to the storage of documents in electronic format. Electronic copies should be password-protected or stored in a password-protected folder or drive for backup purposes.

4. Change History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	3.0		**Abi Loose**	• **See 9.2. Change of provision of Reader Consent from e-consenting portal to OnlineSurvey** • **See 21. Addition of new information about phased opening of study sites**