Study Title: An assessment of the impact of **CONT**rast **EN**hance**D** Spectral Mammography (CESM) on patient management and comparison with MRI (CONTEND Study)

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1. PROTOCOL SIGNATURES:

I give my approval for the attached protocol entitled 'An assessment of the impact of Contrast Enhanced Spectral Mammography (CESM) on patient management and comparison with MRI (CONTEND Study)' dated 24th March 2015.

Chief Investigator

Name: Professor Fiona J Gilbert

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled 'An assessment of the impact of Contrast Enhanced Spectral Mammography (CESM) on patient management and comparison with MRI (CONTEND Study)', dated 24th March 2015 and agree to abide by all provisions set forth therein.

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

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

Principal Investigator

Name:

Signature: _____

Date: _____

Principal Investigator

Name:

Signature: _____

Date: _____

2. AMENDMENT HISTORY

List details of all protocol amendments here whenever a new version of the protocol is produced.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
01	2.0	11.05.15	Lorraine Tucker	Insertion of text to Section 5, Study design, page 8, following peer review.
02	3.0	02.09.15	Lorraine Tucker	Following provisional opinion from REC: Removal of all reference to Stage-1:Pre-Pilot.
02	3.0	02.09.15	Lorraine Tucker	Following provisional opinion from REC: Amendments to flow chart (page 24) and patient contrast questionnaire (page 25).
02	3.0	02.09.15	Lorraine Tucker	Following provisional opinion from REC: Amendments to 9.1, Serious Adverse Effects.
03	4.0	24.02.16	Fiona J Gilbert	Change of trial coordinator
03	4.0	24.02.16	Fiona J Gilbert	Change of contrast agent and risk profile
03	4.0	24.02.16	Fiona J Gilbert	Contact name changes on PIS and consent form.
03	4.0	24.02.16	Paula Willsher	In accordance with trust policy an additional question has been added to the patient contrast questionnaire

3. TABLE OF CONTENTS

4. ABBREVIATIONS

CBU	Cambridge Breast Unit (including Cambridge Breast Cancer Research Unit)
CESM	Contrast Enhanced Spectral Mammography
CRF	Case Report Form
CT	Computed Tomography
GP	General Practitioner
GCP	Good Clinical Practice
ID	Identification
LCC	Left cranio-caudal view
LMLO	Left medio-lateral oblique view
MDT	Multi-disciplinary Team Meeting
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
RCC	Right cranio-caudal view
REC	Research Ethics Committee
RMLO	Right medio-lateral oblique view
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event

5. STUDY SYNOPSIS

Study Title	An assessment of the impact of **CONT**rast **EN**hance**D** Spectral Mammography (CESM) on patient management and comparison with MRI (CONTEND Study)
Internal ref. no.	RADIOL/2015/CONTEND
Study Design	The aim of this pilot study is to establish the Contrast Enhanced Spectral Mammography (CESM) technique and study procedures. Results of this pilot and feedback from staff will inform Phase 2 of the study which will be a larger, multi-centre, randomised control trial. The study will be undertaken by members of the Cambridge Breast Unit (CBU) at Addenbrooke's Hospital, Cambridge using CESM technology provided by GE Healthcare as an upgrade to the GE Senographe Essential digital mammography system. This technology is already established throughout the world and has FDA approval and is CE marked. This will be a randomised, sequential cohort study. Following standard mammography and ultrasound all women with lesions of suspicion 3, 4 or 5 will be randomised to either receive CESM in addition to their assessment procedure or to receive usual care. Sealed envelopes will be held at CBU reception desk containing either 'CESM' or 'Usual Care' and one will be selected at random to determine to which arm of the study the woman is allocated. After providing informed consent, those women randomised to receive CESM will undergo the procedure either during the same clinic visit or on a day following the initial clinic visit. This will be dependent upon clinic time and staff availability and the woman's own preferences / circumstances. The index lesion and any additional disease detected by CESM will be biopsied as appropriate and results will be discussed at the multi-disciplinary meeting (MDT). For those with biopsy confirmed disease a decision will be made at that meeting regarding conservation surgery, mastectomy or neo-adjuvant therapy. For those with benign disease confirmed by core biopsy standard care will be followed.

	MRI will be performed on appropriate women in line with standard practice. Additional disease detected by MRI will be biopsied if this will influence patient management. Biopsies will be undertaken using either ultrasound or MRI guidance. These cases will be discussed at the MDT and a decision made regarding conservation surgery, mastectomy or neo-adjuvant therapy. The pathway for women randomised to receive usual care will be the same as for those randomised to receive CESM, excluding the CESM procedure, i.e. they will undergo biopsy during their initial clinic visit and results will be discussed at the MDT where a decision regarding their future management will be made. A flowchart illustrating patient pathways during the CONTEND Study can be found in Appendix I of this document. A proforma will be used for each case to record patient pathway, results of biopsies and MDT patient management decisions. Staff will be asked to provide feedback on patient acceptability and ease of undertaking the CESM procedure. They will also be asked to record any incidents of note, e.g. patient related problems; impact on clinic; issues with equipment. Time taken to undertake the examination will be recorded. In order to compare the diagnostic accuracy of CESM with MRI, CESM images and MRI images will be anonymised and read by different readers - CESM images will be reported without the knowledge of the MRI results and vice versa. Mammography and ultrasound images will be available. A completed report on a proforma will be the basis for statistical analysis. Histopathology data collected following surgery or from core biopsy if surgery is not undertaken and will be used as the gold standard for measurement of tumour size and extent of disease. If the patient is having primary drug therapy, tumour size will be determined from the mammogram.
Study Participants	Women attending CBU who have lesions of suspicion 3, 4 or 5 following routine mammography and ultrasound.

Planned Sample Size	50 patients with successful CESM examinations will be required to establish the technique, study procedures and to provide sufficient data to inform further study. It is estimated, due to randomisation procedure, approximately 100 patients will need to be recruited in order to obtain this number.
Planned Study Period	Recruitment to the study is planned to run for 12 months or until sufficient number of participants has been accrued. The study will end once data analysis is complete.
Primary Objective	To assess the impact the addition of CESM has on patient management.
Secondary Objectives	To compare the sensitivity and specificity of CESM with MRI.
Primary Endpoint	The detection of additional disease by CESM that changes patient management. Analysis will be undertaken to determine the impact of CESM on patient management decisions (actual or hypothetical). These will be extracted from details recorded on the proforma.
Secondary Endpoints	Secondary endpoints are the sensitivity and specificity of CESM and MRI on a per lesion basis – including comparison of the maximum dimension of the index tumour – as assessed by independent readers and compared with surgical histopathology. The efficacy of each technique at detecting additional lesions and the number of false positives identified by each will also be determined. False positives will be confirmed through follow up at 6 months. Analysis of results will inform further study, e.g. sample size and power calculations, and will include an assessment of clinical technique and study procedures from staff questionnaires.

6. BACKGROUND AND RATIONALE

The advent of digital mammography has presented opportunities for new technologies and techniques to be developed within the field of breast disease diagnosis. One such technology is Contrast Enhanced Spectral Mammography (CESM).

CESM is a technique intended for use as an adjunct following inconclusive mammography and ultrasound examinations. Contrast enhanced images are produced using an x-ray specific contrast media (dye) commonly used for CT scans which is injected intravenously into the patient's arm. A conventional mammography machine – similar or the same as the one on which a woman's initial mammogram would have been taken - is modified to take two images at different x-ray exposures in each of the four standard mammographic views (RCC, RMLO, LMLO, LCC). The first exposure is low energy and the second is high energy. The fully automated procedure creates a standard mammographic image and also produces a contrast enhanced image in exactly the same position with the background subtracted out. This reduces image noise and helps to highlight lesions. The whole procedure from injection of contrast media to production of images takes less than 10 minutes.

Potentially, clinical applications for this technique include clarification of mammographic equivocal lesions, detection of occult lesions and determination of extent of disease. Published studies also indicate that contrast enhanced mammography could play an important role in imaging breasts where dense overlapping tissue can present difficulties when viewing standard mammograms [1,2].

Summary of literature

There are few published studies comparing diagnostic accuracy of CESM with MRI in patients with newly diagnosed breast cancer. Most published data are a small sub-study of investigations comparing CESM with conventional mammography and/or ultrasound. Studies generally report detectability, multi-focality, correct diagnosis and compare size measurement for extent of tumour against surgical histopathology. Badr et al [3] discussed the implementation of CESM into routine clinical practice. They stated it was easier and quicker to access than MRI but that a disadvantage is being unable to perform a biopsy during the procedure.

Results from two studies comparing mammography plus CESM with mammography plus ultrasound support the view that CESM may be comparable with MRI [4,5]. They show CESM improves sensitivity without decreasing specificity, provides a better estimation of extent of tumour and is more effective at demonstrating additional foci than both mammography alone

and mammography plus ultrasound. In 2013 Lobbes et al published a summary on contrast enhanced mammography techniques and studies to date [6]. They also concluded contrast enhanced mammography had been shown to be better at detecting breast cancer than mammography - and may be similar to MRI - though MRI may be better for multi-focal disease. Conclusive findings were limited by small study populations and larger studies need to be conducted in order to produce more definitive results.

In a recent study comparing the diagnostic accuracy of CESM with mammography in patients referred from a breast screening programme – which included a cohort of 24 patients who had breast MRI - good agreement was found between tumour size measured by CESM, MRI and histopathology [7]. Previous studies comparing assessment of tumour size include a pilot study of 20 patients which showed the correlation between assessed tumour diameters using CESM and histopathology to be good [8] and one in which 142 breast lesions were evaluated by mammography, ultrasound and CESM [5].

Two studies which do directly compare the diagnostic accuracy of CESM with MRI have been reported recently. Jochelson et al studied 52 patients, measuring maximum diameter of the index (main) tumour on imaging [9]. Of the 52 lesions, conventional mammography detected 42 and both MRI and CESM detected 50. CESM was accurate for tumour extent in all but 2 index lesions, whereas MRI gave accurate size estimation for all. Jochelson et al concluded that CESM detected known primary tumours at a rate comparable to that of MRI (both 96%) and higher than that of conventional digital mammography (81%). CESM had a lower sensitivity (56%) for detecting additional cancers than MRI (88%), but the specificity was higher. On the other hand MRI found 13 false positive cases, 8 having surgery for ultimately benign change, whereas CESM found 2 false positives, not requiring surgery.

In the second study, Fallenberg et al also reported on the detection of breast cancer and tumour size assessment for CESM compared with MRI [10]. They studied 80 patients with newly diagnosed breast cancer of which there was post-op histology for 59. Images were reviewed by an independent reader blinded to other findings. All index tumours (100%) were detected by CESM, 77 (97.4%) by MRI and 66 (82.5%) by conventional mammography. In the correlation of tumour size measurements, there were significant differences between both CESM and MRI compared to mammography. Between CESM and MRI there was no significant difference observed. The best correlation was between CESM and histopathology. There was no evaluation of additional lesions reported.

CESM is a developing technology and the optimum design of equipment and mechanism is still under debate. The addition of digital breast tomosynthesis (DBT) to CESM should further enhance the performance of CESM compared to MRI. Schmitzberger et al (2011) successfully demonstrated the clinical feasibility of CESM DBT as a diagnostic tool but stated

further studies were needed to assess diagnostic sensitivity and specificity [11].

Rationale

Treatment options for women with proven invasive breast cancer depend on the size of the tumour and the presence and location of any additional disease [12]. Breast MRI, using MRI specific contrast media, is currently recognised as the most sensitive imaging technique in determining the extent of disease identified on mammogram or by ultrasound. This means the patient can go straight to definitive surgery rather than having surgical under treatment, i.e. the identification of additional disease may mean the woman has a mastectomy rather than a wide local excision (lumpectomy).

There are several disadvantages of MRI. It is usually performed in a different department from mammography and ultrasound, which can pose problems with accessibility and may delay patient care. Image acquisition takes an average of 40 minutes and the whole procedure can take up to 90 minutes. MRI is also known to produce a higher frequency of false positives than conventional mammography and this can lead to unnecessary surgery and patient anxiety. Some patients may be excluded from undergoing MRI due to claustrophobia or presence of metal within their body. In the UK, MRI is currently used selectively, based on NICE guidelines [13]. There are also economic considerations - MRI is expensive.

CESM is being heralded as a diagnostically comparable, less labour-intensive and cost effective technique to breast MRI. Like MRI, CESM can be used to identify lesions not seen on mammography or ultrasound and to assess the size of lesions and stage of disease. The procedure can be performed on the same day using the same equipment and in the same department as a woman's initial clinic visit. This should reduce patient anxiety and has the potential of a definitive decision on patient management being made earlier in the patient pathway. CESM also has the potential to be used as a screening tool in certain groups of women which is not clinically viable with MRI.

The purpose of this study is to refine the CESM technique, assess acceptability of the test and recruitment levels, establish study procedures and examine effect of CESM on patient management decisions. We also hope to demonstrate an increase in sensitivity and specificity compared to MRI. Analysis of results will inform further study, including power calculations. On completion of this project we intend to apply to the UK NIHR Health Technology Assessment Programme for funding to undertake a multicentre trial comparing the diagnostic accuracy of CESM with MRI (perhaps with an extension to CESM DBT if this

technique becomes available and minimally proven in terms of clinical performance and workflow).

7. OBJECTIVES

7.1 Primary objective

To assess the impact the addition of CESM has on patient management. The hypothesis is that CESM should afford a definitive management decision earlier in the patient pathway.

7.2 Secondary objectives

To compare the sensitivity and specificity of CESM with MRI. Analysis will include:

- index lesion size
- detection of additional lesions
- detection of lesions in contralateral breast
- total extent of disease
- number of false positives identified

8. STUDY DESIGN

8.1 Summary of Study Design

This study will be a sequential cohort study with participants randomised to receive either the addition of CESM or standard care. All women with lesions of suspicion 3, 4 or 5 following mammography and ultrasound will be eligible.

Number of Centres

This will be a single centre study performed by members of the CBU at Addenbrooke's Hospital, Cambridge.

Number of Subjects

We plan to include 100 subjects in this study – approximately 50 to receive CESM and 50 to receive usual care.

Trial duration

Subjects will be recruited into the study following their routine assessment results consultation. Participation in the study will end once the patient has undergone CESM procedure and is returned to standard care. Target recruitment is estimated to take approximately 12 months and the study will end once data analysis is complete.

Subject withdrawal criteria

Subjects that suffer ill-effects from contrast media or procedure, or are unable to complete the procedure for whatever reason, will be withdrawn from the study. Data held on subjects who are withdrawn and on those who elect to withdraw from study will not be used in analysis.

8.2 Primary and Secondary Endpoints/Outcome Measures

The primary endpoint is the detection of additional disease that changes patient management. Analysis will be undertaken to determine the impact of CESM on patient management decisions (actual or hypothetical). These will be extracted from details recorded on the proforma.

Secondary endpoints are the sensitivity and specificity of CESM and MRI on a per lesion basis - including comparison of the maximum dimension of the index tumour - as assessed by independent readers and compared with surgical histopathology. The efficacy of each technique at detecting additional lesions and the number of false positives identified by each will also be determined.

8.3 Study Participants

8.3.1 Overall Description of Study Participants

Participants in the study will be women aged 18 and above with a lesion of suspicion 3, 4 or 5 following mammography and ultrasound.

8.3.2 Inclusion Criteria

To be included in the study the patient must:

- Be willing and able to give written informed consent for participation in the study.
- Be female, aged 18 years or above.

8.3.3 Exclusion Criteria

The presence of any of the following will preclude patient inclusion:

- Known or suspected pregnancy
- Breast implant
- Previous breast cancer
- Known renal impairment
- History of anaphylactoid or anaphylactic reaction to any contrast media

- Contrast media within 24 hours prior to CESM
- Commencement of neo-adjavant chemotherapy, hormone treatment, radiotherapy or surgery for this episode

8.4 Study Procedures

Screening and enrolment

Patients who have been identified as suitable for the study will be approached at the routine post-biopsy consultation when their diagnosis and treatment plan is being discussed. At this meeting, patients will be given both written and verbal information about the study.

If a patient wishes to enter the study, their eligibility will be checked by a Research Radiographer or Research Nurse and signed informed consent will be obtained. The patient will then be randomised and if she is in the CESM arm an appointment will be arranged for the procedure.

CESM procedure

Patients will be given an intravenous injection (via a power injector), into their arm, of an iodine based contrast media. This type of contrast media is used routinely in CT imaging procedures and the Cambridge University Hospitals NHS Trust Patient Group Directive for its administration will be adhered to. Patients will be asked to complete the Patient Contrast Questionnaire prior to the procedure (see Appendix II) and have their creatinine level checked using a Point of Care (PoC) device in the CT department. If serum creatinine is elevated >150 mmol/l the procedure will not be performed.

Two minutes after the injection, two mammographic exposures will be taken automatically, within approximately one second of each other, in each of the standard mammographic views (RCC, RMLO, LCC, LMLO).

Assessment of CESM images

Paired images will be examined to see if the tumour has been enhanced by the contrast media and to assess its extent. Images will also be assessed for additional foci and contralateral lesions.

Comparison of CESM and MRI

CESM images and MRI images will be anonymised and read by different readers - CESM images will be reported without the knowledge of the MRI results and vice versa. Mammography and ultrasound images will be available. A completed report on a proforma will be the basis for statistical analysis.

Analysis

Analysis will be undertaken to determine the impact of CESM on patient management decisions (actual or hypothetical). These will be extracted from details recorded on the proforma.

We will also compare the sensitivity and specificity of CESM and MRI on a per lesion basis - including comparison of the maximum dimension of the index tumour - as assessed by independent readers and compared with surgical histopathology.

Analysis of results will also be undertaken in order to inform further study, e.g. sample size and power calculations, and will include an assessment of clinical technique and study procedures from staff questionnaires.

8.4.1 Informed Consent

Eligible patients for this study will be identified in the out-patient clinic by members of the breast team. Patients will be given written and verbal information about the study. Consent will be taken by experienced Research Radiographer or Research Nurse. Following their CESM imaging, patients will return to normal standard of care. Safety reporting requirements will end 72 hours after the procedure.

8.4.2 Definition of End of Study

The study will end once the last patient recruited has undergone surgery and the surgical histopathology results are available.

9. SAFETY REPORTING

9.1 Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

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

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

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

After injection into an artery or vein, it is uncommon (1% risk = 1-10 in 1,0000) to experience pain and discomfort

Rare effects (0.1% risk=1-10 in 10,000) include diarrhoea, irregular heartbeat, kidney problems, cough, fever, general discomfort or dizziness

Very rare (0.01%=less than1in 10,000) include seizures (fits), clouding consciousness, disturbance of senses like touch, trembling, flushing, difficulty breathing including severe breathing difficulty due to fluid in the lungs, short term brain disorders (encephalopathy), short term memory loss, coma and stupor or myocardial infarction .

Any allergic or anaphylactic reactions to the contrast media used in CESM are likely to occur soon after the injection. These will be managed according to local policies by members of the breast team. Minor reactions, e.g..skin rashes, hives (urticaria), itching (pruritus), nausea, dizziness, runny nose (rhinorrhea), brief retching and /or vomiting will be monitored until symptoms have alleviated or further action is needed.

Moderate reactions,e.g. headache, persistent vomiting, wheezing (mild bronchospasm), palpitations, facial swelling, raised blood pressure (hypertension), abdominal cramps; may require an injection of antihistamine and/or adrenaline. An emergency drugs pack will be available in the room during CESM procedures for this purpose.

In the exceptional event of a serious reaction which has the potential to be life-threatening, e.g. difficulty breathing (overt bronchospasm), chest pain, irregular heartbeat (arrhythmia), collapse, seizure, cardiac arrest; a ‘crash’ call will be made to summon the emergency medical team.

9.2 Reporting Procedures for Serious Adverse Events

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

9.3 Expected Adverse Events

The following adverse events are known possible side effects of CESM procedure. They are generally not serious in nature and will not be recorded as part of this study.

- Bruising from site of injection
- Allergic reaction to contrast media

10. STATISTICS

10.1 The Number of Participants

There will be approximately 100 participants in order to provide 50 who will undergo CESM.

10.2 Analysis of Endpoints

Data from all eligible subjects will be included in the analyses. These will be patients for whom we have data from MRI, CESM and surgical histopathology.

Statistical significance of differences between CESM and MRI will be calculated using McNemar's test [14]. Receiver operating characteristic (ROC) curves will be constructed for both imaging modalities.

Agreement between maximum lesion diameter based on CESM and MRI or CESM and histopathology will be expressed in Bland-Altman plots.

11. ETHICS

11.1 Consent

The Informed Consent form will be approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements. The investigator will ensure that each

study participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with their participation.

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

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

11.2 Ethical Committee Review

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

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

11.3 Protocol Amendments

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

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

11.4 Declaration of Helsinki and Good Clinical Practice

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

11.5 GCP Training

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

12. DATA HANDLING AND RECORD KEEPING

12.1 Case Report Form

All data will be transferred into a Case Report Form (CRF) which will be anonymised. All study data in the CRF will be extracted from and be consistent with the relevant source documents. The CRFs will be completed, dated and signed by the investigator or designee in a timely manner. It will remain the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to study coordinator, data manager and the investigators as required.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used. Changes must not be made to the CRF pages once the original has been returned to the study coordination centre.

12.2 Source Data

To enable peer review, monitoring, audit and/or inspection investigators must agree to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages. Source data will include CSEM, MRI and histopathology reports.

12.3 Electronic Data Storage

All study data will be entered into a database administered by University of Cambridge. The participants will be identified by a study specific participants number and/or code - their name or any other identifying details will not be included in any study data electronic file.

12.4 Data Protection & Patient Confidentiality

All investigators and site staff involved in this study must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The study

staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so. Study data will be stored for 10 years.

13. FINANCING AND INSURANCE

The trial will be sponsored jointly by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The study will be funded by a grant from GE Healthcare,

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising thorough participation in the clinical trial.

14. PROTOCOL COMPLIANCES AND BREACHES OF GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

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

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

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

15. PUBLICATIONS POLICY

Ownership of the data arising from this trial resides with the study team. The investigators have complete control over data. On completion of the study the data will be analysed and tabulated and a report prepared. GE Healthcare will not have the right to review data prior to publication. All data and images collected during the study and made available to GE Healthcare following publication will be anonymised to comply with data protection and patient confidentiality. Funding from GE Healthcare will be acknowledged within publications.

16. REFERENCES

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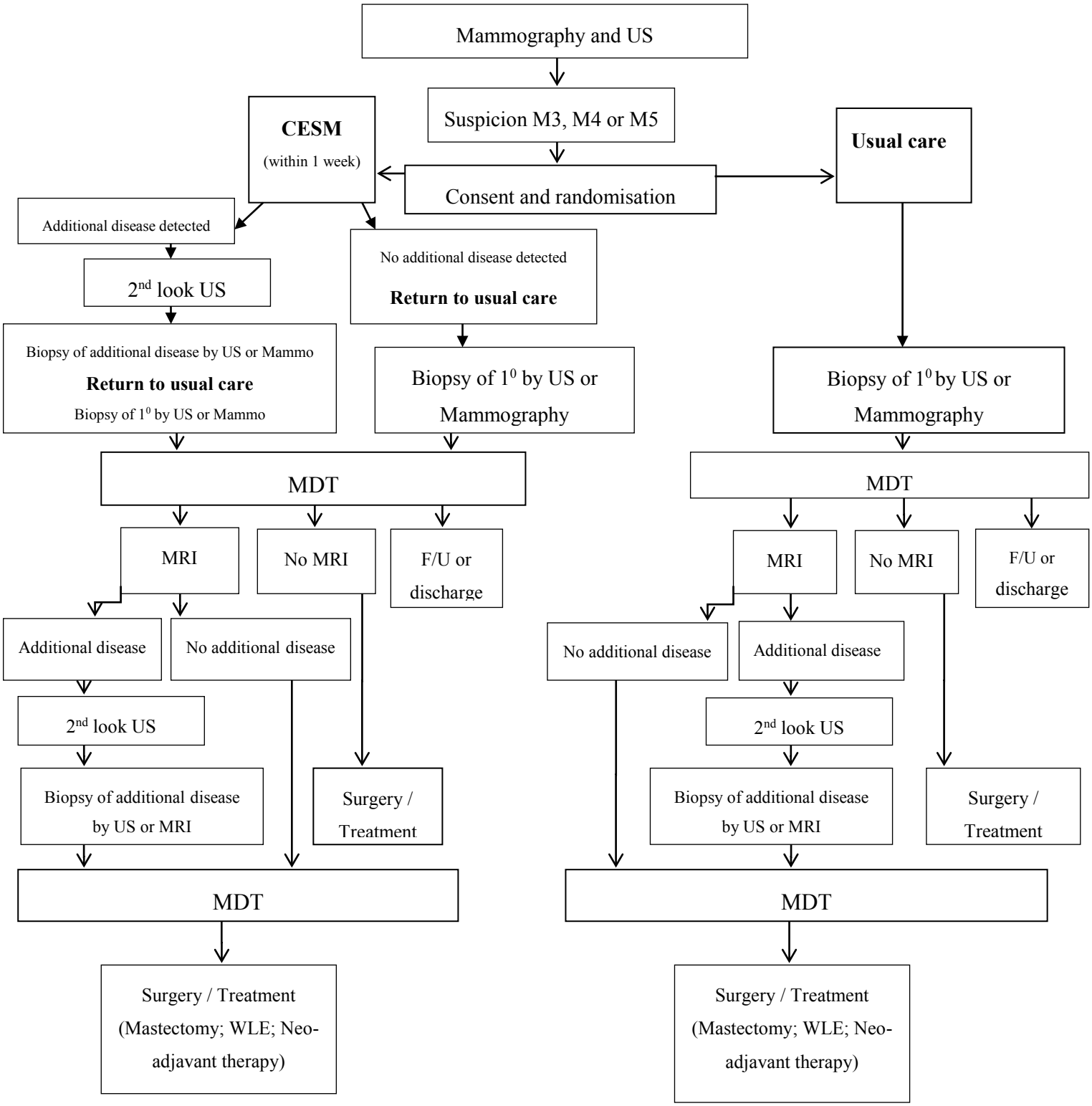
17. APPENDICES

I. Patient pathways during CONTEND Study

II. Patient Contrast Questionnaire



Patient pathways during CONTEND study

US	Ultrasound
MDT	Multidisciplinary Team Meeting
F/U	Follow up
WLE	Wide Local Excision

Affix patient ID label here:

CONTEND study

Patient contrast questionnaire

As part of the Contrast Enhanced Spectral Mammography (CESM) procedure, we are seeking your permission to administer an injection of contrast medium (dye) as part of your examination.

We need to ask you the following questions prior to your injection:		
Have you had injections of contrast medium in any past examinations in x-ray?	Yes	No
If yes, did you have any problems related to this injection?	Yes	No
If yes, please state:		
Are you allergic to anything?	Yes	No
If yes, please state:		
Do you have asthma?	Yes	No
Are you diabetic?	Yes	No
If you are diabetic, do you take metformin?	Yes	No
Do you have an overactive thyroid? (hyperthyroidism)	Yes	No
Are you on interleukin 2 therapy?	Yes	No
Do you suffer from sickle cell anaemia?	Yes	No
Do you suffer from Chronic Kidney Disease (CKD)?	Yes	No

Do you suffer from any brain pathology? Tumour, epilepsy, seizures?	Yes	No
If yes, are you currently taking any medication for this? Please state: ……	Yes	No
Please state the date of the first day of your last menstrual period: ~~Please state the date of the first day of your last menstrual period:~~		
Is there any chance you might be pregnant?	Yes	No
Do you use oral contraceptive pill?	Yes	No
Do you take hormone replacement therapy (HRT)?	Yes	No

Please do not sign this form until you are with the radiographer.		
Print name	Signature	Date

For official use only		
Date of blood test:	eGFR:	Serum creatinine:

Practitioner	Signature	Date
