IRAS Project ID: 237233

Study Protocol

CONTrast Enhanced breaSt Tomosynthesis (CONTEST) in patients suspected of having breast cancer: a prospective comparison with digital mammography and breast MRI

Study Acronym	**CONTEST**
Sponsor	**University of Dundee and NHS Tayside**
Sponsor R&D Number	2017ON01
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Chief Investigator	Ms Patsy Whelehan
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PROTOCOL APPROVAL

Contrast enhanced breast tomosynthesis in patients suspected of having breast cancer: a prospective comparison with digital mammography and breast MRI.

Signatures
The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Ms Patsy Whelehan Chief Investigator	Signature:	Date:
Prof Graham Ball Individual Responsible for Statistical Review	Signature:	Date:
Dr Sarah Vinnicombe Co-Investigator	Signature:	Date:

LIST OF ABBREVIATIONS

AE	Adverse Event
AUROC	Area Under the Receiver Operating Characteristic Curve
BI-RADS	Breast Imaging and Reporting Data System
BPE	Background Parenchymal Enhancement
CE-DBT	Contrast-Enhanced Digital Breast Tomosynthesis
CESM	Contrast-Enhanced Spectral Mammography
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
DBT	Digital Breast Tomosynthesis
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DM	Digital Mammography
DMC	Data Monitoring Committee
DMS	Data Management System
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
HRA	Health Research Authority
HRT	Hormone Replacement Therapy
IF	Incidental Findings
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
NCTIMP	Non-Clinical Trials of Investigational Medicinal Products
NHS	National Health Service
OCP	Oral Contraceptive Pill
PI	Principal Investigator
PIS	Patient Information Sheet
REC	Research Ethics Committee
ROC	Receiver Operator Characteristic
SAE	Serious Adverse Event
SOP	Standard Operating Procedures
SMG	Study Management Group
TASC	Tayside Medical Science Centre
US	Ultrasound
VAS	Visual Analogue Scale

SUMMARY/SYNOPSIS

Study Title	CONTrast Enhanced breaSt Tomosynthesis (CONTEST) in patients suspected of having breast cancer: a prospective comparison with digital mammography and breast MRI	
Study Design	Prospective non-randomised paired comparison of CE-DBT and breast MRI	
Study Population	Consented symptomatic women attending the Breast Clinic with clinical suspicion of breast cancer	
Sample Size	200 women	
Planned Study Period	3 years	
Clinical Phase Duration	2 years	
Follow-up Phase Duration	None	
Primary	Objectives To assess the incremental diagnostic performance of CE-DBT over DM in the diagnosis of breast cancer	Outcome Measures Sensitivity of CE-DBT compared with DM using surgical pathology as the gold standard
Secondary	Objectives To assess the accuracy of local staging of breast cancer with CE-DBT compared with DM, US and MRI	Outcome Measures Correlation of tumour size measurements and identification of multifocality with CE-DBT compared to MRI, using surgical pathology as the gold standard
Inclusion Criteria	Women aged 18 to 70 years old with clinical suspicion of breast cancer	
Exclusion Criteria	Women unable to undergo CE-DBT Women unable to undergo breast MRI Women with locally advanced cancer who are likely to receive neoadjuvant chemotherapy Women with severe comorbidities precluding surgical treatment	

1 INTRODUCTION

It is well established that digital mammography (DM) has limitations in the diagnosis of breast cancer in both symptomatic and screening populations[1]. This is largely attributable to obscuration of masses by overlapping normal fibroglandular parenchyma, particularly in women with dense breasts, seen in up to 40% of Scottish women. Even with state-of-the-art DM, sensitivity in the dense breast can be under 60%[2]. In the symptomatic clinic setting, diagnostic uncertainty about the presence and extent of breast cancer can persist, even after complementary breast ultrasound. This can necessitate subsequent supplemental tests such as breast magnetic resonance imaging (MRI) to allow treatment planning.

The shortfalls of DM have been partly addressed by development of two novel mammographic techniques.

Digital breast tomosynthesis (DBT) is a quasi-3D mammographic technique, which improves visibility of malignant structural features, particularly spiculation. Its ability to resolve composite opacities also increases specificity compared with DM. Published studies show increased cancer detection rates of 20-30%, with a concurrent reduction in recall rates in the screening setting[3]. Research by our group and others has established that DBT can accurately characterise indeterminate mammographic abnormalities detected at screening[4].

Contrast-enhanced spectral mammography (CESM) is a 2D mammographic technique yielding functional information on the vascularity of breast lesions through dual energy subtraction. It enables the neovascularisation of malignant tumours to be detected. The diagnostic accuracy of CESM in the literature is better than DM and comparable to MRI, with sensitivities over 90%[5-7]. This is despite the fact that timings of image acquisition after contrast medium administration are quite different between CESM and MRI.

Spiculation, the feature highlighted by DBT, is most frequently seen in low grade, relatively indolent breast cancers[8]. Conversely, the pathological process underpinning visualisation of tumours at CESM, neoangiogenesis, is more pronounced in aggressive high grade cancers, which may appear paradoxically benign at DM and DBT[9].

CE-DBT is a new imaging modality combining the structural and functional information from DBT and CESM (manufactured by Hologic^{R} and CE marked; Selenia Dimensions with *i-View* software) respectively into a single, short examination, depicting the entire biological spectrum of breast cancer. It can be performed quickly and economically in the outpatient breast clinic, so could provide a major step forward in prompt one-stop characterisation of breast lesions without recourse to breast MRI. Though MRI is the gold standard in breast cancer detection and local staging, it is difficult to access in a timely fashion, expensive and time consuming. In many patients, it is either contraindicated (e.g. in patients with pacemakers), not tolerated, or - increasingly - not possible because of body habitus. CE-DBT could therefore represent an effective, cost-efficient alternative to MRI.

2 BACKGROUND & RATIONALE

Increasing pressure on diagnostic services in Scotland poses challenges to timely diagnosis and local staging of breast cancer. Between 20 and 40% of women in Scotland have dense breast tissue, rendering assessment with conventional imaging problematical. The need for supplemental tests such as MRI incurs substantial delays in treatment planning, risking additional anxiety and distress for our patients, and increased costs. CE-DBT could obviate the need for further tests in many patients. Breast cancer charities are reluctant to fund studies of novel imaging tests requiring expenditure on equipment/software, and a study such as the one proposed here is essential before a multicentre study with full health economic evaluation can be carried out.

Demonstration of superior accuracy of CE-DBT over DM would have profound implications for the diagnostic work-up of women suspected of having breast cancer, especially where DM has limitations (invasive lobular cancers, mammographically occult cancers, imaging and/or clinical size discrepancies). The ability to diagnose more reliably the entire spectrum of breast cancers

in a single examination at the initial clinic visit, would greatly speed up the diagnostic pathway for many patients. Since mammography is generally performed prior to ultrasound (US), CE-DBT could prompt immediate ultrasonographic assessment of all areas of potential disease in both breasts, ensuring timely, thorough diagnostic work-up without recourse to further tests. This would reduce patient anxiety, inconvenience, and service costs, while speeding up treatment planning.

As CE-DBT is an entirely novel technique, no pilot data are available. However, one small study from elsewhere used a prototype CE-DBT unit that is not currently available[10]. In this study of only 36 invasive cancers, there was no significant difference in the diagnostic performances of MRI, CESM or CE-DBT, but even with such small numbers, all three techniques significantly outperformed 2D DM.

There is, however, good evidence from the literature on the incremental diagnostic accuracy of DBT and CESM over DM. CESM increases the sensitivity of DM by up to 20%[5,6,11,12] and in a recent meta-analysis had an overall sensitivity of 98%[13]. In the screening setting, DBT results in incremental breast cancer detection rates of 3.9 per 1000 screens in women with dense breasts, with lower recall rates (23/1000 screens)[14]. A comparative study of DM, DBT and MRI showed that both the latter are more accurate than DM in lesion sizing and evaluation of tumour extent[15].
Thus, the key research questions are:
a) Does CE-DBT improve upon the diagnostic accuracy of DM in women presenting with symptoms suspicious of breast cancer? (the primary objective)
b) Is local staging (lesion size, focality assessment, prediction of invasive and in situ disease) with CE-DBT sufficiently accurate to obviate the need for breast MRI? (the secondary objective).

Additional research questions include:
c) Whether patient-related factors such as mammographic density and age influence the performance of CE-DBT
d) Does background parenchymal enhancement (BPE) occur as frequently as in breast MRI and does it impair interpretation of CE-DBT, as it can with MRI[16]?
e) Identification of any histological features affecting the comparative accuracy of CE-DBT compared with breast MRI.

3 STUDY OBJECTIVES & OUTCOMES

The aim of this study is to evaluate the performance of CE-DBT in the identification and local staging of symptomatic breast cancer. The primary objective is to determine the incremental increase in sensitivity of CE-DBT over DM alone in women with symptoms/signs suspicious for breast cancer, the latter currently being standard of care. This will be assessed through comparison with post-surgical pathology in all women with biopsy-proven breast cancer treated with primary surgery.

The second objective is to assess the accuracy of local cancer staging with CE-DBT regarding extent and the presence/ absence of multifocality. All patients with biopsy-proven breast cancer will undergo breast MRI, since this is the current imaging gold standard and a head to head comparison of CE-DBT and MRI against surgical pathology will be made.

Thirdly, planned subset analysis will explore the influence of age, breast density, and BPE on the diagnostic performance of CE-DBT. In order to address this, participants will undergo CESM of the index breast at two time points to enable semi-quantitative kinetic analysis of lesional and background contrast enhancement in comparison to breast MRI to determine whether this affects diagnostic performance.

Finally the study will explore the accuracy of CE-DBT in the subset of women who would normally receive pre-operative breast MRI as standard of care and will aim to identify clinicopathological features influencing the accuracy of CE-DBT in a planned subset analysis.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	Outcome Measure:	Timepoint of outcome measured
Diagnostic performance of CE-DBT in the diagnosis of breast cancer	Incremental sensitivity of CE-DBT versus DM, compared to gold-standard surgical pathology	Final 6 months of study

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	Outcome Measure:	Timepoint of outcome measured
Assessment of comparative accuracy of CE-DBT and MRI in local staging of breast cancer	Variance between CE-DBT, MRI and pathology	Final 6 months of study
Comparison of specificity of CE-DBT versus breast MRI at breast level	Number of false positive examinations (score 3 or above) with each imaging modality	Final 6 months of study
Comparative accuracy of CE-DBT and MRI in women who would normally have preoperative MRI	Subgroup analysis (invasive lobular cancers, clinical-imaging size discrepancy, mammographically occult cancer): AUROC curve analysis of diagnostic accuracy	Final 6 months of study
Evaluation of clinicopathological factors affecting performance of CE-DBT	Subgroup analysis by: age, breast density, BPE, histology. AUROC analysis	Final 6 months of study

4 STUDY DESIGN

4.1 INTERVENTION

This is a paired comparison study of a novel diagnostic test (CE-DBT) i.e. all participants will receive the equivalent of standard care (DM) and the experimental procedure (CE-DBT). A proportion of the recruits will also undergo breast MRI as a study-specific procedure. The duration is intended to be 36 months, with 24 months of that consisting of the recruitment period. Eligible patients will be invited to participate on attendance at the symptomatic clinics. No follow up of participants is involved after all the study-related imaging is complete, but the majority of the data collection will be undertaken during retrospective image analysis. Outcomes will be measured once all data collection is complete (see above). *See flowchart (section 4.3).*

4.2 STUDY DESCRIPTION

In this paired imaging comparison study, female patients aged 18-70 years with clinical features of operable breast cancer (suspicion levels 4 and 5) will be consecutively recruited from symptomatic breast clinics to undergo this novel diagnostic test instead of standard digital mammography, DM.
The clinician carrying out the initial consultation will determine whether there is strong clinical suspicion of breast cancer and will pre-screen for comorbidities or other factors that preclude

primary surgical treatment (see section 4.12). The study manager (or a delegated member of staff) will check for the safety of administering iodinated contrast media and any contraindications to MRI during the consent interview. The upper age limit reflects the higher incidence of asymptomatic renal impairment over 70 years.

After informed consent, participants will undergo CE-DBT in the clinic, with ultrasound and biopsy according to standard clinical practice. The participant will have a cannula inserted into a dorsal hand vein or an antecubital vein by a trained practitioner with the patient seated. Iodinated contrast material will be injected intravenously using a power injector after patients have been informed about sensations (e.g. a feeling of warmth throughout the body, a metallic taste in the mouth). Three minutes after the injection, imaging in the CE-DBT unit will commence. The order of image acquisition will be as follows:

i. **Index breast: MLO CE-DBT (CESM then DBT), CC CE-DBT (CESM then DBT)**
ii. **Contralateral breast: CC CE-DBT (CESM then DBT), MLO CE-DBT (CESM then DBT)**
iii. **Index breast: MLO CESM ONLY**

The participants will be observed for 15-20 minutes after the procedure and the cannula left in place during this period in case of delayed contrast reactions.

All images will then be read prospectively in the clinic as below and the CRF filled in. Subsequently patients will undergo biopsy as dictated by the clinical and CE-DBT findings according to standard NHS clinical protocols.

Prior to surgery and within 3 weeks of recruitment, all women with biopsy-proven breast cancer planned for immediate surgery will undergo contrast-enhanced MRI.

Reading protocol:
Readers in the study must be accredited in mammography image interpretation and have undergone DBT and CESM interpretation training at a recognised centre. All the reading radiologists will be on a delegation log.

The three components of the CE-DBT studies will be read in strict sequential order by the radiologist running the clinic according to a standardised procedure detailed on the CRF.

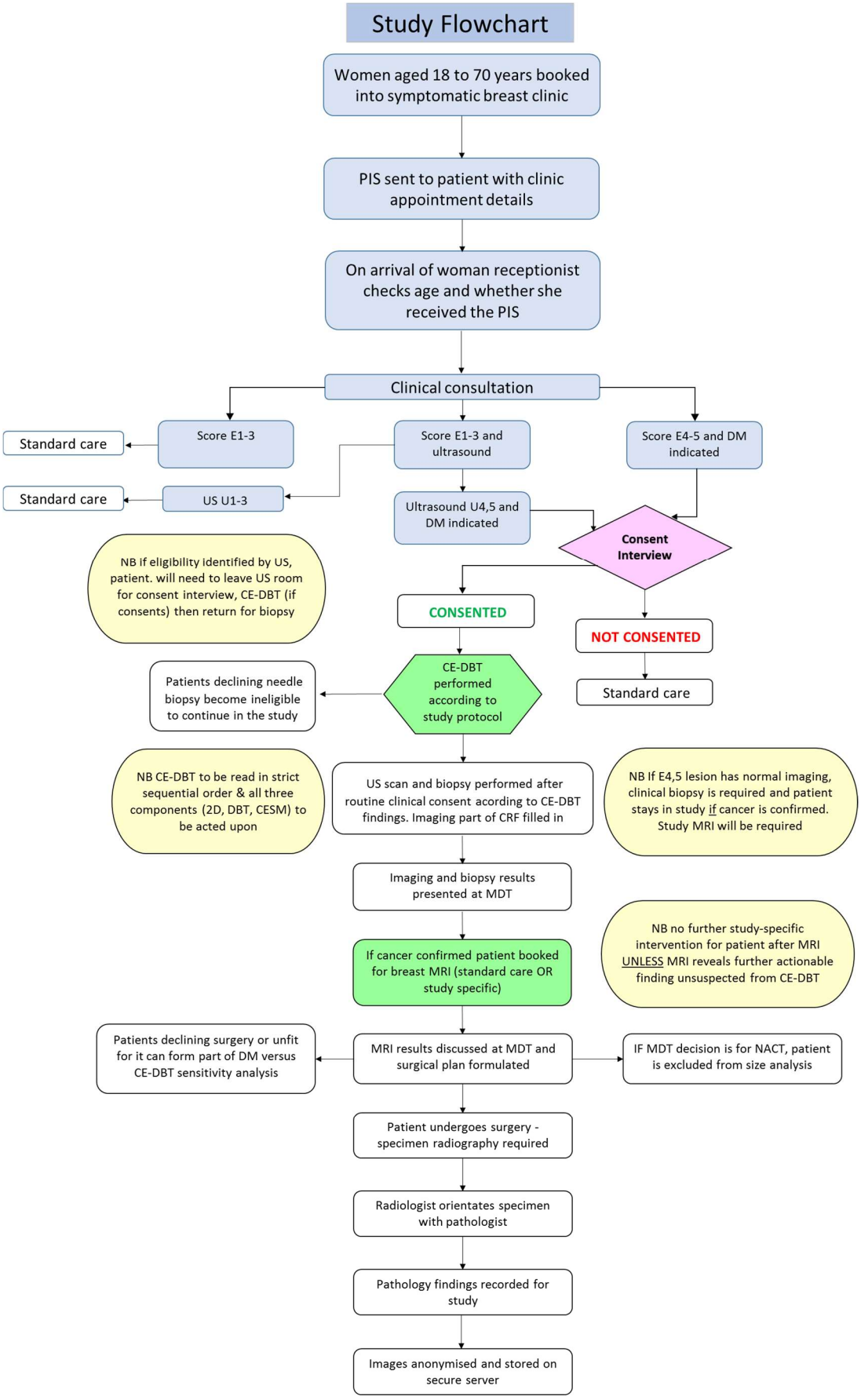
The radiologist will carry out ultrasound of the breast according to the CE-DBT findings and carry out biopsies according to standard clinical practice. The ultrasound findings will be documented on the CRF by the reporting radiologist.

During or immediately after the clinic, the CE-DBT images will be read by a second radiologist in the same strict order using the CE-DBT reading protocol, as part of standard double reading. Lesion signal intensity will be measured on the workstation for generation of signal intensity-time curves.

MRI scans will be read by a third radiologist blinded to CE-DBT and ultrasound findings, but aware of the clinical and DM findings, (i.e. identical conditions to those under which CE-DBT will be read). MRI features, size, suspicion level and location of lesions will be documented. Background parenchymal enhancement of both breasts will be categorised according to the BIRADS 5th edition lexicon[18]. Lesion signal intensity-time curves will be generated for subsequent comparison with CESM images.

Prior to surgery, preoperative discussion with the reporting pathologist, and careful documentation, will take place at the breast multidisciplinary team (MDT) meeting to allow precise correlation between abnormal foci of enhancement on MRI, CE-DBT and histology. Orientated specimen radiography will be performed on all wide local excision specimens. Formal analysis will take place in the last six months of the study after recruitment is complete.

4.3 STUDY FLOWCHART



4.4 STUDY MATRIX

At the point of receipt of the GP referral letter all patients aged 18-70 years will be sent details of their Breast Clinic appointment and this will contain a PIS about the study.

Upon clinic attendance the receptionist will check the age of the patient and whether she received the PIS. However, if they have not received the PIS then they will be handed a copy by the receptionist. They will be given enough time to read the PIS and ask any questions prior to taking informed consent. The clinician examining the patient will note whether examination is suspicious or diagnostic of breast cancer (E4 or E5). If there are no obvious indications for primary or neoadjuvant chemotherapy, the patient will then undergo the consent interview usually by the study manager (or a delegated member of staff). Patients who do not consent will undergo standard care. Consenting patients will have CE-DBT. The components of the CE-DBT will be read in defined order by the radiologist running the clinic, who will fill in the case report form (CRF). The patient will proceed to ultrasound (US) and biopsy as dictated by the clinical and imaging findings, after which the relevant section of the CRF will be completed.

Note that patients may also be recruited if they have suspicious findings on ultrasound. In these circumstances, the patient will leave the US room for the consent interview.

All patients with biopsy-proven cancer will undergo breast magnetic resonance imaging (MRI) within three weeks of the clinic visit. As approximately 30% of patients would undergo MRI as standard of care this will be an additional intervention in 70% of patients.

	Clinic appt. details	**Clinic visit**	**MDT meeting**	**1-3 weeks post - MDT**	**MDT meeting**	**1-2 months post - MRI**	**1 month post - surgery**
PIS	X	X*					
Inclusion/exclusion		X					
Consent		X					
Intervention (CE-DBT)		X					
Patient questionnaire (1)		X					
US and biopsy		X					
Histology review			X				
MRI				X			
MRI results review					X		
Patient questionnaire (2)				X			
Surgery						X	
Data collection							X

***if not received with clinic appointment letter**

4.5 STUDY ASSESSMENTS

The study specific assessment is primarily reading of the CE-DBT study in strict order, so that the incremental diagnostic benefit of the DBT and CE components of the study over standard DM can be assessed. The reading protocol is detailed below.

The three components of the CE-DBT studies will be read in strict sequential order by the radiologist running the clinic according to a standardised procedure detailed on the CRF as follows:

1. The low energy 2D images (shown to be equivalent to standard DM[17] and hereafter referred to as DM) will be read, the findings documented and assigned a BI-RADS suspicion score (1- Normal to 5- Malignant).

2. The radiologist will assess breast density on the DM images using visual analogue scales (VAS) and BI-RADS (5th edition) density categorisation[18]. Raw 2D images will undergo automated volumetric density assessment with Volpara®.

3. The DBT images will next be read by the same radiologist; any lesions identified will have features, size, location and BI-RADS suspicion level recorded.

4. The high energy subtracted (CESM) images will be read and findings documented as above. For all lesions, enhancement will be graded (mild, moderate or marked).
5. Background parenchymal enhancement of both breasts will be assessed and assigned a categorical score (none, mild, moderate, marked).

During or immediately after the clinic, the CE-DBT images will be read by a second radiologist in the same strict order as part of standard double reading. Using the first and second index breast MLO CESM subtracted images, lesion signal intensity will be measured on the workstation for generation of signal intensity-time curves.

A brief questionnaire will be completed by the recruit after the CE-DBT to collect information on experience of the procedure, including the presence/absence of any minor contrast reactions. This will include free text boxes as well as a small number of validated questions. This will be collected with the CRF.

Similarly after the MRI, the same simple questionnaire will be completed to assess women's experience of the MRI scan.

4.6 STUDY SAFETY ASSESSMENTS

CE-DBT safety – these relate primarily to the administration of iodinated intravenous contrast material. As clinically occult renal impairment is commoner in the elderly, women over 70 will not be recruited. The clinician examining the patient will obtain the patient's medical history and screen eligible women for any of the exclusion criteria listed above (known renal failure, a history of contrast reactions, severe comorbidities that would preclude surgical treatment, contraindications to breast MRI etc.). At the start of the CE-DBT procedure an intravenous cannula will be inserted into an antecubital vein and this will stay in place for the duration of the procedure and for approximately 20 minutes afterwards, so that in the unlikely event of a severe contrast reaction, intravenous access is already established[19].
Should any adverse reaction occur during or immediately after the CE-DBT study (for example, a contrast reaction), safety assessments would include monitoring of blood pressure, pulse and airway patency. A resuscitation trolley will be available, as in any other part of the radiology department where intravenous contrast is administered. All relevant staff groups will have received training in the management of contrast reactions.

Radiation dose – the additional radiation dose arising from participation in the study has been assessed by a Medical Physics Expert and the following assessment made:

The study uses CE-DBT for the assessment of symptomatic abnormalities that are highly suspicious for breast cancer. Analysis of data from the NHS Tayside clinics has shown that 75% of such women will prove to have cancer. Their standard radiological work-up would include 2-view DM and the occasional patient might also require coned magnification views. The low energy component of the CE-DBT study has been shown to have equivalent diagnostic accuracy and radiation dose to standard DM and thus will obviate the need for additional standard care DM. The dose from a two-view digital examination is expressed as the Mean

Glandular Dose and is approximately 4.5mGy per breast, taken as 75th percentile of MGD from local patient dose audit (personal communication – NHS Tayside Medical Physics Expert MPE and Scottish Breast Screening Programme Radiation Protection Advisor). Standard care results in a minimum of 2 DM views per breast taken as 4.5mGy per breast plus any additional dose arising from magnification views.

In this study, patients will receive additional 2-view high energy images and 2-view DBT of each breast. An additional oblique view CESM will be performed on the index breast only, as detailed in the image acquisition protocol.

It should be noted that all recruited patients are likely to directly benefit from this test because of greater diagnostic confidence in the presence or absence of breast cancer in women with strong clinical suspicion of the disease.

Additional Dose
The high energy component of the CE-DBT examination imparts a radiation dose of approximately 35% of the DM exposure. The additional dose arising from the high energy component is therefore 1.6 mGy to the contralateral breast. The index breast receives a repeat CESM Oblique exposure, resulting in an additional dose to this breast of 4.7mGy from all high energy CESM exposures.

DBT utilises a number of low dose exposures at a range of angles to build a sliced 3D picture of the breast. The dose from Hologic DBT is estimated as 10% higher than the Hologic DM exposure (UKMPG 2016 presentation on patient dose survey results), thus the additional dose per 2 view DBT is estimated as 5mGy to each breast.

Thus, it is estimated that a participant will receive a total mean glandular dose of 14mGy to their index breast and 11mGy to the contralateral breast. Of this, 4.5mGy to each breast is considered as standard care. Thus a participant will receive an additional dose of 9.7 mGy and 6.6 mGy to the index and contralateral breasts respectively.

Risks
Taking the average age of the participants as 50 years, the risk of radiation induced breast cancers is 14 per million women per mGy[20]. Thus the approximate risks to this cohort are estimated at:

1 in 5000 from the total radiation dose, where the additional risk is 1 in 7000.

This is in a cohort who actually have a 75% chance of already having breast cancer. The natural lifetime risk of developing breast cancer is approximately 1 in 8 (CRUK website). These additional doses are commensurate with the doses received by asymptomatic women attending for breast screening once every three years.

Biopsy safety – standard local NHS clinical procedures apply. There are no study-specific biopsy procedures.

MRI safety - standard NHS clinical procedures apply. Renal function is assessed as part of the safety review prior to contrast MRI. eGFR will be assessed using centre clinical procedures and participants will proceed to contrast MRI if all other eligibility criteria are met.

No specific safety assessments will be required for the study provided the screening process has excluded the possibility of severe renal impairment and any history of prior severe contrast reactions or iodine allergy.

4.7 TISSUE

No study-specific research tissue or blood samples will be required. Biopsies will be taken as standard care according to the clinical and imaging findings. However, in the case of biopsies being precipitated by additional findings on CE-DBT, not seen on DM, this will be recorded on the CRF.

It is Unit policy for all patients undergoing biopsy of a suspicious finding to be consented for additional research samples taken during the diagnostic biopsy in case of eligibility for ongoing trials in the Breast Unit. Participation in CONTEST will not preclude this.

The only tissue collected will be image-guided sampling of any suspicious abnormality in the breast and/or axilla as dictated by standard clinical practice. No study-specific tissue samples are required.

4.8 INCIDENTAL FINDINGS

In the unlikely event of any incidental findings (IF: previously undiagnosed condition) considered to be clinically significant, these will be reported to the participant's GP and/or consultant by the Principal Investigator (PI), with the consent of the participant.

4.9 STUDY POPULATION

The study population is women aged 18-70 years referred to the symptomatic Breast Clinic with symptoms or signs suggestive of breast cancer.

4.10 NUMBER OF PARTICIPANTS

The study aims to recruit 200 women with clinical suspicion of breast cancer. Analysis of data from the symptomatic clinics at Ninewells Breast Unit (NHS Tayside) shows that around 75% of these (150) will subsequently prove to have breast cancer on biopsy. With a conservative estimated consent rate of 50% and screen failure rate of between 10-20% this equates to a recruitment rate of one to two patients per week over 2 years, the anticipated recruitment period.

4.11 INCLUSION CRITERIA

- Age 18 to 70 years inclusive
- Female
- Clinical examination findings suspicious or typical of operable breast cancer (E4/5)
- **AND/OR**
- Ultrasound findings suspicious or typical of malignancy (U4/5)
- **AND** able to give informed consent

4.12 EXCLUSION CRITERIA

Individuals will not be enrolled to the study if they are participating in the clinical phase of another interventional study or have done so within the last 30 days. Individuals who are participating in the follow-up phase of another interventional study, or who are enrolled in an observational study, will be co-enrolled where the CIs of each study agree that it is appropriate.

Initial screening will be performed by the clinician performing the initial consultation, as past medical and surgical history and comorbidities will be assessed as standard care.

Study-specific exclusion criteria are as follows:

1. History of prior iodinated contrast reaction
2. Iodine allergy
3. Severe asthma
4. Known renal impairment, strong risk factors for renal disease
5. Previous breast cancer surgery to ipsilateral breast or implants
6. Current pregnancy, lactation
7. Inflammatory or clinically obvious locally advanced (inoperable) primary breast cancer who are likely to receive neoadjuvant chemotherapy (in these patients, imaging/pathological correlation will not be possible)
8. Contraindication to MRI
9. Obvious severe comorbidities precluding operative treatment
10. Otherwise deemed to be unsuitable by the clinical team

5 PARTICIPANT SELECTION AND ENROLMENT

All women booked into the new patient clinics having been referred with breast symptoms will be sent the study information in the Patient Information Sheet (PIS) with the clinic appointment letter. On the woman's arrival at the clinic, the age of the patient and receipt of the study information will be checked at reception. Where information has not been received, they will be given a copy of the PIS by the receptionist. They will be given enough time to read the PIS and ask any questions prior to taking informed consent.

5.1 IDENTIFYING PARTICIPANTS

Patients will be invited to a consent interview with a suitably qualified and delegated member of the clinical or research team (GCP trained) if they are found during the clinic to fit the inclusion criteria. If they attend the consent interview and decide to enter the study they will be asked to sign a consent form.

5.2 CONSENTING PARTICIPANTS

The informed consent process will be conducted in compliance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical research.
As indicated above, potential recruits will be consented by a trained member of staff, usually the study manager (or a delegated member of staff), during the Breast clinic. As the PIS will have been sent out with appointment details, all women will have had the opportunity to consider the study information prior to attendance at the clinic. However, if a patient has not received the PIS then they will be handed a copy by the receptionist when they check in for their appointment. Enough time will be given for them to read the PIS and ask any questions prior to taking informed consent.
Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the appropriate person will be asked for their consent. In all cases the CI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

5.3 SCREENING FOR ELIGIBILITY

There will be three opportunities to screen potential participants, firstly from the GP referral letter, secondly at clinical examination and consultation and thirdly, at ultrasound examination if a mammogram has not already been performed.

- Participants screened in by the clinician (E4-5, mammography indicated) will be referred for consent interview.

Patients not screened in by the clinician but who proceed to ultrasound can be screened in by the radiologist/advanced practitioner (U4-5, mammography indicated) and referred for consent interview after the ultrasound scan.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible patients and non-recruited patients will receive standard care in the clinic. A screening log will be kept, detailing enrolled and screen fail patients, along with eligible patients who decline to participate following a consent interview, with reasons if given.

5.5 WITHDRAWAL PROCEDURES

- Participants will be withdrawn if the CE-DBT examination is not completed.
- Any women declining needle biopsy will be withdrawn from the study because it will not be possible to determine a definitive diagnosis.
- Participants:
    - Who, after a diagnosis of breast cancer, prove unsuitable for initial surgical treatment (severe co-morbidities), or
    - Who decline surgery, or
    - Where initial surgical treatment does not occur (e.g. neoadjuvant chemotherapy to allow breast conservation)

  Will be excluded from further analysis because full pathological-radiological correlation will not be possible.

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

Data will be collected on the paper CRF during the clinic. The study manager (or a delegated member of staff) will check for completeness during or as soon as possible after the clinic. Subsequently data will be entered into an electronic database (see below). The CRF will have been designed with the help of the study statistician.

Data from subsequent MRI scans will also be recorded on the CRF, as will the postoperative pathology data.

The data collection forms will be piloted using data from the first ten participants recruited. Demographic and medical data will be collected from the clinical notes by the study manager (or a delegated member of staff). Imaging data will be recorded on the paper CRF by the reporting radiologists (volumetric breast density data will be recorded at a later date after the pseudonymised raw images have been run through the volumetric breast density software, Volpara™). Results of all biopsies will be recorded after the MDT meeting by the study manager (or a delegated member of staff) with the help of the relevant radiologist as necessary.

For all cancer cases, the MRI findings will be recorded on the CRF by the reporting radiologist. Subsequent postoperative histology will be collected by the study manager (or a delegated member of staff) from the MDT meeting records and ICE pathology records and recorded on the CRF.

All data from the paper CRFs will entered into an electronic database by the study manager. Hard copy and electronic data will be stored securely to maintain data security and patient confidentiality.

Data collected will include:

- Demographic data: age, weight, height, menstrual status, date of last menstrual period if premenopausal, OCP or HRT use
- Clinical findings, nature, location and suspicion score
- Relevant medical history
- Radiology findings for DM, DBT, CESM components of the CE-DBT examination with location, suspicion level and size of each lesion identified
- Breast density assessment (BI-RADS category, VAS score and Volpara™)
- Ultrasound findings with location, suspicion score, size
- Biopsy results
- MRI findings
- Surgical pathology findings

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP53 Data Management Systems in Clinical Research.
The data management system (DMS) will be Microsoft Access, as approved by Sponsor. The Breast Imaging Research Group has a purpose designed secure Access-based database, BRIGID, in which data will be stored. This database has a built-in audit trail.
After patient recruitment is complete, relevant data for analysis will be sent to the study statistician after pseudonymisation either via a secure encrypted drive or electronically.
The DMS will be based on the protocol and CRF for the study and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the study and to ensure the eligibility and safety of the participant. The study database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.

The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 1998, which brought UK law into line with the EU Data Protection Directive. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the study team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases, after recruitment when all relevant data has been collected.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

The proposed study is necessarily exploratory given the novelty of the CE-DBT technique. An achievable sample size has been set based on data from the symptomatic breast clinic at Ninewells Hospital (NHS Tayside), where approximately 75% of women with clinically suspicious symptoms and signs prove to have breast cancer. Thus, a consented cohort of 200 women including 150 with cancer is realistic and achievable. Our recent study (as yet unpublished) of DBT in the symptomatic setting has shown a 15% gain in sensitivity over DM in dense breasts. From the literature, CESM has a sensitivity over 90%[11-13].

Thus, assuming a sensitivity for DM of 70%, the CI and study statistician calculate that a sample size of 120 is adequately powered to show an increase in sensitivity of CE-DBT of 10%.

Allowing for a 10-20% examination contraindication rate, it is considered that there will be enough participants - 150 with cancer - covering a sufficient range of characteristics (e.g. lobular cancer [12% of symptomatic invasive cancers in women under 70 in our practice], mammographically occult cancer) to enable us to advance knowledge concerning the most promising applications of CE-DBT, and to generate sufficient preliminary data for robust power calculations using appropriate models (TT test and Chi squared power models) for subsequent full-scale clinical effectiveness and cost-effectiveness studies.

It is challenging to maximise recruitment to studies within a busy clinical service, but we have considerable experience of overcoming such challenges. Multidisciplinary communication and co-ordination are key to success and we are fortunate in having a population of patients who are very interested in participating in research, even without perceived benefit to themselves. At least 4 clinically suspicious cancers are seen per week, representing 75% of all clinically suspicious presentations. Thus 200 participants (150 with cancer) could be recruited over two years assuming a 50% consent rate.

7.2 PROPOSED ANALYSES

Formal analysis will take place in the last six months of the study after recruitment is complete.

Analysis will require 4 months of expert statistical input. Professor Graham Ball, Professor of Bioinformatics at Nottingham Trent University, has great expertise in cancer systems biology, identification of biomarkers, development of prognostic indices and application of statistics to medical diagnostics. At the start of the study he will oversee design of the case report forms to ensure that all relevant data fields are captured and he will carry out data analysis in the final quarter of the study.

Analysis:
1) Comparing incremental sensitivity and specificity between DM and CE-DBT:
True and false positive and negative rates in comparison with histopathology will be computed for each modality, at individual lesion level. BIRADS 1&2 will be considered negative and 3-5, positive. Shifts in BIRADS classifications between modalities will be analysed, to identify differences in diagnostic certainty. Receiver Operator Characteristic curves will be utilised as a standard for evaluation of classification performance.

2) Comparing performance between CE-DBT and MRI for local staging:
Malignant lesions classified as unifocal: measurement accuracy will be compared (whole tumour diameter variance in mm from histological size). Diagnostic accuracy for additional lesions (not detected clinically or seen at initial diagnostic DM) will be compared between CE-DBT and MRI using the methods described in #1.

3) The analyses described above will be applied to explore variations in differential performance between CE-DBT and MRI:
a) by breast density
b) by age
c) by levels of BPE
d) by tumour subtype (invasive lobular versus invasive ductal carcinomas)

We will explore enhancement intensity and temporal patterns of enhancement according to histopathological tumour type and grade.

7.3 MISSING DATA

Every effort will be made to chase up missing data, failing this any patient with essential data missing will be excluded from the analysis.

Patients will be withdrawn if they do not complete the full CE-DBT protocol or if they fail to proceed directly to surgical treatment. Failure to tolerate the MRI will not necessarily result in the patient being withdrawn, as it will still be possible to compare CE-DBT findings with the gold standard surgical pathology.

7.4 TRANSFER OF DATA Statistical analysis will necessitate secure transfer of anonymised data taken from the secure server housing the electronic case report forms to the study statistician.

8 STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 STUDY MANAGEMENT GROUP

The study will be co-ordinated by a Study Management Group (SMG), consisting of the CI, study manager, senior trial manager and co-investigators, with the study statistician if necessary and meeting on a monthly basis. The remit of the SMG will include review of day-to-day management of the study, recruitment rates and any problems encountered, according to TCTU protocol.

8.2 STUDY STEERING COMMITTEE

A Study Steering Committee is not required for this non-randomised study and the SMG will subsume this role. However, the CI may point seek advice from an external adviser with the relevant clinical expertise.

8.3 DATA MONITORING COMMITTEE

As this is a small study, data monitoring will be the responsibility of the Study Management Group.

8.4 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHST R&D approval will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not

disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

9.3 DATA PROTECTION

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

9.4 INSURANCE AND INDEMNITY

The University of Dundee and Tayside Health Board are Co-Sponsoring the study.

Insurance – The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.

Where the study involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

10 ADVERSE EVENTS

10.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

10.2 RECORDING AND REPORTING AE

All SAEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate. The occurrence of minor contrast reactions will also be recorded.

SAEs will be recorded from the time a participant consents to join the study until the participant's last study visit, which will generally be for the study-specific MRI examination.

The Investigator will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from the study due to what he or she perceives as an intolerable AE; for example, if the patient is unable to tolerate the MRI examination. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. SAEs will be followed up until 30 days after participant's last visit. Any adverse events will largely be those related to the administration of intravenous contrast material and are expected to occur within 24-48 hours of administration of intravenous contrast. Clinical progression of the cancer, or hospitalisation for elective treatment (planned before joining the study) will not be classed as SAEs.

The CI or delegate will ask about the occurrence of AEs/SAEs at every visit during the study, which will include the initial clinic visit and the visit for the MRI scan. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHST R&D Office for review and approval.

In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

12.2 STUDY RECORD RETENTION

Archiving of study documents will be for ten years after the end of study.

The Breast Imaging Research Group has designed and set up a purpose-built repository for storing anonymised multimodality images from research patients (after appropriate consent). This Imaging Bank is hosted by the College of Life Sciences at the University of Dundee.

12.3 END OF STUDY

The end of study is defined as database lock. The Sponsor or CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

The findings of the study will also be relayed to the participants and a lay summary of the findings will be publicised.

13.3 PEER REVIEW

This study is has been adopted by the TCTU as an approved study and has been subject to TCTU review, Research Governance review and ongoing support from TASC in its development and oversight.

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