

# MR Imaging as an Additional Screening Modality for the Detection of Breast Cancer in Women Aged 50–75 Years with Extremely Dense Breasts: The DENSE Trial Study Design<sup>1</sup>

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Women with extremely dense breasts have an increased risk of breast cancer and lower mammographic tumor detectability. Nevertheless, in most countries, these women are currently screened with mammography only. Magnetic resonance (MR) imaging has the potential to improve breast cancer detection at an early stage because of its higher sensitivity. However, MR imaging is more expensive and is expected to be accompanied by an increase in the number of false-positive results and, possibly, an increase in overdiagnosis. To study the additional value of MR imaging, a randomized controlled trial (RCT) design is needed in which one group undergoes mammography and the other group undergoes mammography and MR imaging. With this design, it is possible to determine the proportion of interval cancers within each study arm. For this to be an effective screening strategy, the additional cancers detected at MR imaging screening must be accompanied by a subsequent reduction in interval cancers. The Dense Tissue and Early Breast Neoplasm Screening, or DENSE, trial is a multicenter RCT performed in the Dutch biennial population-based screening program (subject age range, 50–75 years). The study was approved by the Dutch Minister of Health, Welfare and Sport. In this study, mammographic density is measured by using a fully automated volumetric method. Participants with extremely dense breasts (American College of Radiology breast density category 4) and a negative result at mammography (Breast Imaging Recording and Data System category 1 or 2) are randomly assigned to undergo additional MR imaging ( $n = 7237$ ) or to be treated according to current practice ( $n = 28948$ ). Participants provide written informed consent before the MR imaging examination, which consists of dynamic breast MR imaging with gadolinium-based contrast medium and is intended to be performed for three consecutive screening rounds. The primary outcome is the difference in the proportions of interval cancers between the study arms. Secondary outcomes are the number of MR imaging screening-detected cancers, proportions of false-positive results, diagnostic yield of MR imaging, tumor characteristics, quality of life, and cost effectiveness.

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In the Netherlands, women between the ages of 50 and 75 years are screened for breast cancer every 2 years by using mammography. Since the implementation of the national breast cancer screening program, breast cancer mortality has decreased by approximately 30% (1). This can be ascribed to a combination of early tumor detection and an improvement in therapy in the course of time (2). Nevertheless, among screening participants, approximately one-third of breast cancers are diagnosed between screening rounds (ie, are interval cancers) (1). Interval cancers have a worse prognosis compared with screening-detected breast cancers, with 5-year survival rates of 78% and 95%, respectively (3). Results of previous studies (4,5) have shown that the sensitivity of mammography is markedly reduced in women with breasts that have high mammographic density, resulting in the highest interval cancer rate occurring in

women with extremely dense breasts. Breast density is a function of the relative amounts of fibroglandular (dense) tissue and fat (transparent) tissue in the breast (6,7). The lower sensitivity of mammography in women with dense breasts is most likely caused by a masking effect due to the high amount of fibroglandular tissue (4). In addition, mammographic density is one of the stronger breast cancer risk factors (8,9). Women with extremely dense breasts have a three- to sixfold higher breast cancer risk compared with women with entirely fatty breasts (8) and a twofold higher risk compared with the screening population average, which is approximately halfway between the categories scattered and heterogeneously dense (10).

In high-risk populations, magnetic resonance (MR) imaging has proven to be a more sensitive screening method than mammography or ultrasonography (US) (11–15). A meta-analysis of published studies among women at high risk for breast cancer (eg, women with a *BRCA1* or *BRCA2* mutation or a strong family history of breast cancer) showed a sensitivity estimate of 94% (95% confidence interval [CI]: 90%, 97%) and a specificity estimate of 77.2% (95% CI: 74.7%, 79.7%) for the combination of mammography and MR imaging, compared with, respectively, 39% (95% CI: 37%, 41%) and 94.7% (95% CI: 93.0%, 96.5%) for mammography alone (13). The combination of mammography and MR imaging was more effective than MR imaging alone because, in most studies, mammography had a higher rate of detection of ductal carcinoma in situ than MR imaging (16).

The effectiveness of MR imaging screening in women who have no apparent risk factors other than having

extremely dense breasts is unknown. The only study on this topic, to our knowledge, is a substudy of the ACRIN 6666 trial (17) that included women with heterogeneously or extremely dense breasts who had at least one other risk factor. These women had already been screened annually with mammography and US for three consecutive screening rounds. The study reported a sensitivity of 31.3% (95% CI: 11.0%, 58.7%) for mammography alone, which increased to 100% by adding MR imaging (95% CI: 79.4%, 100%). However, the increase in sensitivity was accompanied by a reduction in specificity for mammography (92.1% [95% CI: 89.7%, 94.1%]) and for mammography combined with MR imaging (70.6% [95% CI: 66.8%, 74.3%]). It should be noted that the sample size of the group undergoing MR imaging was limited, comprising 612 participants.

A methodologic disadvantage of previous studies on the effectiveness of supplementary MR imaging in high-risk groups is that all study participants underwent imaging with all techniques being studied (11–13). As a

### Advances in Knowledge

- The Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial is a parallel-group randomized controlled trial to investigate the effectiveness and cost-effectiveness of screening with mammography and MR imaging compared with those of mammography alone in 50–75-year-old participants in a Dutch breast cancer screening cohort with extremely dense breasts.
- For the trial to find evidence that the additional screening-detected cancers do not represent overdiagnosed breast cancers, a subsequent reduction in interval cancers is required, which is the primary end point of DENSE.
- In addition, several secondary outcomes will be assessed, including the number of MR imaging screening-detected cancers, the proportion of false-positive results, the diagnostic yield of MR imaging, tumor characteristics, quality of life, and cost-effectiveness.

### Implication for Patient Care

- If it is shown that additional screening with MR imaging improves breast cancer detection at an early stage, less-invasive treatments will be needed in some patients.

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### Abbreviations:

ACR = American College of Radiology  
 BI-RADS = Breast Imaging Reporting and Data System  
 CI = confidence interval  
 DENSE = Dense Tissue and Early Breast Neoplasm Screening

### Author contributions:

Guarantors of integrity of entire study, P.H.M.P., K.M.D., C.H.v.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, M.J.E., M.F.B., C.E.L., M.D.F.d.J., J.V., M.A.A.J.v.d.B., E.M.M., W.B.V., C.H.v.G.; clinical studies, M.J.E., M.F.B., P.H.M.P., C.E.L., M.D.F.d.J., R.H.C.B., J.V., K.M.D., M.B.I.L., R.M.P., E.M.M., W.P.Th.M.M., W.B.V., C.H.v.G.; experimental studies, M.D.F.d.J., N.K.; statistical analysis, M.J.E., M.F.B., P.H.M.P., M.D.F.d.J., M.A.A.J.v.d.B., E.M.M., C.H.v.G.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

consequence, these investigations were not able to evaluate whether there was a reduction in interval cancers, as the only interval cancers were those that neither test detected. Although study results show that MR imaging added to screening mammography helps find more cancers, a subsequent reduction in interval cancers is a precondition of effectiveness, because this represents clinically relevant cancer detection, rather than the overdiagnosis that may explain part of the higher numbers of screening-detected cases (18). To study the additional value of MR imaging by its effect on interval cancer rate, a randomized controlled trial design is needed, with one group undergoing mammography and the other group undergoing mammography and MR imaging.

In this report, we describe the rationale and design of Dense Tissue and Early Breast Neoplasm Screening (DENSE), a trial designed to investigate the effectiveness and cost-effectiveness of screening with mammography and MR imaging compared with those of screening with mammography alone in Dutch breast cancer screening participants with extremely dense breasts.

### Materials and Methods

The study is financially supported by Bayer HealthCare Medical Care. For research purposes, Matakina (Wellington, New Zealand) has provided Volpara Imaging Software, version 1.5 for installation on servers in the screening units of the Dutch screening program. N.K. is shareholder in Matakina, the chief executive officer of and a shareholder in ScreenPoint Medical (Nijmegen, the Netherlands), and a consultant of and shareholder in QView Medical (Los Altos, Calif). R.M.M. serves as a speaker for Siemens and Bayer and receives research support from Siemens and Seno Medical. R.M.P. is a member of the scientific advisory board of Hologic but does not receive financial reimbursement. The other authors will have control of inclusion of any study data and information that might

present a conflict of interest for N.K., R.M.M., and R.M.P.

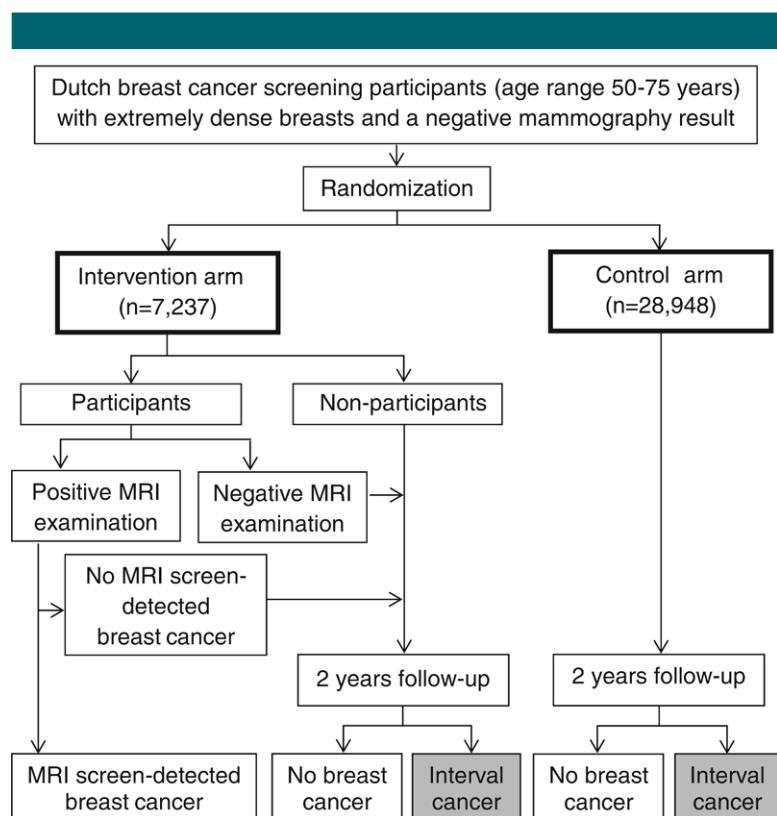
### Study Design

DENSE is a multicenter randomized controlled trial performed in the Dutch biennial screening program. Screening participants with extremely dense breasts (American College of Radiology [ACR] category 4 [19]) and a negative mammography result (Breast Imaging Reporting and Data System [BI-RADS] category 1 or 2) are randomized to either the intervention group ("additional MR imaging examination,"  $n = 7237$ ) or the control group ("current practice,"  $n = 28948$ ) with an allocation ratio of 1:4 (Figure). Randomization is performed centrally according to a computer-generated random schedule in permuted blocks of random block size stratified by hospital and by regional screening organization. After randomization, only those allocated to the intervention arm are asked to participate in the study,

in a so-called single-consent prerandomization design (20). This design was chosen to prevent anxiety and self-referral-induced contamination in the control arm. In several cancer screening trials, the single-consent prerandomization design has already been used (21–25).

The intervention consists of dynamic breast MR imaging with a gadolinium-based contrast medium (gadobutrol, Gadovist; Bayer Healthcare Medical Care, Berlin, Germany) and is intended to be performed for three consecutive screening rounds. Women randomized to the control group undergo usual screening (ie, no further examination until the next mammographic screening examination 2 years later).

On-site monitoring is performed to ensure that the rights and well-being of the participants are protected; that the research data are accurate, complete, and verifiable from source documents; and that the conduct of the study is in



Flowchart of DENSE trial. The flowchart describes only one screening round, but the study is intended to be performed for three consecutive screening rounds.

compliance with the currently approved protocol, good clinical practice, and regulatory requirements (26). An independent data safety monitoring board evaluates the efficacy and safety of the study and recommends whether to continue, modify, or stop the trial.

The study has been approved by the Dutch Minister of Health, Welfare and Sport herein advised by the Health Council of the Netherlands (2011/19 WBO, the Hague, the Netherlands). Ethical approval was obtained on November 11, 2011.

### Study Population

The study population comprises Dutch breast cancer screening participants aged 50–75 years. Women are biennially screened by using full-field digital mammography. Tomosynthesis is not part of their screening study, nor is tomosynthesis used in the screening program. Almost 2.6 million women belong to the target population of the Dutch breast cancer screening program, and approximately 80% actually attend the program (1). As a standard practice, breast cancer screening participants are informed about the exchange of screening data with, for example, the National Cancer Registry and Statistics Netherlands to evaluate the national screening program. Participants who give notice of an objection to this data exchange are not included in the DENSE trial.

In the Netherlands, screening mammography studies are read by dedicated screening radiologists. To be certified as a screening radiologist, a radiologist has to attend an 8-day mammography course at the Dutch reference center for screening and has to interpret a minimum of 3000 mammogram pairs per year. Recertification is required every 5 years. All screening mammograms are independently read by two screening radiologists. In cases of disagreement, the screening radiologists have to reach consensus. If no consensus is reached, a third reader will decide.

Mammographic density is estimated by using a fully automatic and validated method to estimate the (relative) volume of dense tissue in the breast

(Volpara Imaging Software, version 1.5; Matakina). The software has been installed on servers in the screening units of the Dutch screening program, all of which are equipped with digital mammography systems of the same brand (Selenia; Hologic, Bedford, Mass). The software fully automatically estimates breast density volumes from raw full-field digital mammography data. It is based on an algorithm that incorporates physical parameters to estimate the absolute dense volume, absolute breast volume, and their ratio (percentage volumetric density) (27,28).

Several studies have investigated the correlation between BI-RADS density categories determined by radiologists and Volpara Density Grade categories (29–31). Clear associations between the two methods have been reported, although weighted  $\kappa$  coefficients were moderate (0.54 [29] and 0.40 [30]) to good (0.80 [31]). Comparable  $\kappa$  coefficients have been reported for pairwise comparisons of radiologists using BI-RADS density classifications (29). The limitation of comparing the volumetric method with radiologist-determined BI-RADS density is therefore that the result will depend on the radiologists it is compared with. The comparison with breast density estimations from MR imaging are therefore more relevant.

Gubern-Mérida et al (30) validated the Volpara volumetric breast density estimation on full-field digital mammograms by comparing these estimates with volumetric estimates that were obtained from breast MR imaging data ( $n = 186$ ). Pearson correlation coefficients for percentage volumetric density, total breast volume, and dense volume, respectively, were 0.93, 0.97, and 0.85. Wang et al (32) found similar results to Gubern-Mérida. Lately, Volpara has been validated in risk studies, notably those of Eng et al (33) and Brand et al (34). Both studies found evidence that percentage volumetric density measured with Volpara is strongly related with breast cancer risk. The study by Eng et al compared six breast density measurement methods, of which Cumulus and Volpara appeared to be the

most strongly related to breast cancer risk.

The percentage volumetric density values are categorized by using a four-point scale that correlates with the BI-RADS ACR classification, with a score of 1 indicating almost entirely fatty tissue; a score of 2, scattered fibroglandular densities; a score of 3, heterogeneously dense tissue; and a score of 4, extremely dense tissue (19). Approximately 8% of the Dutch screening participants have extremely dense breasts (ACR category 4). The values in the mediolateral oblique and craniocaudal views, as well as those in the left and right breasts, are averaged to obtain the percentage volumetric density per woman. If not all views are available, or if women have breast implants or a pacemaker, the software cannot give a (reliable) estimate.

Women in the intervention arm are excluded in cases of standard contraindications to MR imaging (35), severely impaired renal function (glomerular filtration rate [GFR] < 40 mL/min), a previous adverse reaction to a gadolinium-based contrast agent, pregnancy, claustrophobia, and extreme adiposity (weight > 150 kg). Participants are screened for these MR imaging contraindications by using the standard MR imaging safety screening questionnaire of the University Medical Center Utrecht (Utrecht, the Netherlands). In addition, a self-developed questionnaire is used to screen participants for risk factors for impaired renal function (36–39). The presence of one or more risk factors requires estimated GFR evaluation through point-of-care creatinine testing (i-STAT system; Abbott Point of Care, Princeton, NJ) before the MR imaging examination in the radiology department. An overview of the inclusion and exclusion criteria is given in Table 1.

### Recruitment

Participants are recruited from screening regions that are in the serving area (within 60 km) of the eight hospitals where the MR imaging examinations are performed. Women in the intervention arm receive an invitation letter to participate in the DENSE trial from their



regional screening organization. The invitation letter is accompanied by an extensive information brochure and a reply card. Those who indicate an interest in participation in the study, either through online registration or by returning the reply card, are contacted by phone to determine eligibility for contrast material-enhanced MR imaging. Nonresponders receive a reminder letter from the regional screening organization 3 weeks after initial invitation. The MR imaging examinations are performed in the University Medical Center Utrecht, Antoni van Leeuwenhoek Hospital, Radboud University Medical Center, Jeroen Bosch Hospital, Albert Schweitzer Hospital, Hospital Group Twente (ZGT), VU University Medical Center, and Maastricht University Medical Center. Participants provide written informed consent prior to the MR imaging examination in the radiology department.

### Intervention Group

Participants in the intervention group undergo a breast MR imaging examination, which is intended to be performed for three consecutive screening rounds. All breast MR imaging examinations are performed with a 3.0-T (Achieva or Ingenia) system from Philips or a 3.0-T (Trio, Verio or Skyra) system from Siemens by using a dedicated phased-array bilateral breast coil. All acquisition parameters are detailed in Table 2. In essence, in all participating hospitals, the MR imaging protocol consists of an optional T2-weighted sequence according to standard protocol, a diffusion-weighted sequence, and a dynamic contrast-enhanced T1-weighted sequence. The diffusion-weighted data set is acquired with three *b* values, 0, 50, or 150 and 800 sec/mm<sup>2</sup>, and a maximum in-plane acquisition voxel size of 2.25 × 2.51 mm. In all hospitals, the dynamic contrast-enhanced data set consists of a high-spatial-resolution precontrast series, followed by multiple high-temporal-resolution series during the first 90 seconds after contrast material injection, followed by six high-spatial-resolution series. The high-temporal-resolution series are acquired with a duration between 3.9 and 5.1 seconds and a maximum acquisition voxel size of 2.58 × 2.82 × 6.00 mm.

**Table 1**

DENSE Inclusion and Exclusion Criteria	
Type of Criterion	Criterion
Inclusion	Dutch breast cancer screening participants
	Negative screening mammography result (BI-RADS category 1 or 2)
	Extremely dense breasts (ACR category 4, as determined with Volpara software)
Exclusion	Living within the serving area of the hospital (within a radius of 60 km)
	Notice of an objection to data exchange
Additional exclusion criteria in intervention arm	Institutional care resident
	Intracorporeal metals
	A previous adverse reaction to a gadolinium-based contrast agent
	Severely impaired renal function (glomerular filtration rate < 40 mL/min)
	Pregnancy
	Claustrophobia
	Extreme adiposity (>150 kg)

The high-spatial-resolution series are acquired with a maximum acquisition voxel size of 0.90 × 1.00 × 1.80 mm and such that center k-space of the first series is acquired at or before 120 seconds. Use of a dedicated breast MR imaging computer-aided diagnosis system is compulsory.

MR imaging studies are assessed by a breast radiologist with experience ranging between a minimum of 5 years and a maximum of 23 years. The number of participating radiologists is limited to a maximum of two breast radiologists per participating hospital. MR imaging examinations are assessed according to the BI-RADS MR imaging ACR lexicon, with final MR imaging assessment categories ranging from 1 to 5 (40). In cases of BI-RADS category 3 (“probably benign finding”), independent double reading is performed by a second radiologist who is affiliated with another participating hospital. Potential discrepancies are resolved by consensus. MR imaging BI-RADS category 1 (“negative”) or 2 (“benign finding”) provides no indication for further work-up. In case of a BI-RADS category 3 diagnosis, the MR imaging examination is repeated in 6 months. When the MR imaging data are given a score of BI-RADS category 4 (“suspicious abnormality”) or 5 (“highly suggestive of malignancy”), cytologic or histologic tissue sampling is warranted. Cytologic or histologic biopsy of the lesion seen only at MR imaging is at first performed by

means of targeted US. A marker clip is placed after each US-guided biopsy, with the exception of unequivocally palpable lesions. In cases of benign or otherwise unexpected biopsy results, the biopsy location is confirmed at post-biopsy T1-weighted non-fat-saturated MR imaging, with immediate MR imaging-guided rebiopsy (and histologic examination) in cases of incorrect location. A BI-RADS category 0 score (“incomplete examination”) is a temporary outcome that is assigned only in cases of nondiagnostic MR imaging studies—for example, missing postcontrast series. In these cases, the examination is completed as soon as possible.

### Control Group

The control group represents current practice—that is, mammographic screening every 2 years as part of the national breast cancer screening program. Necessary information from the control group (ie, interval cancer rate, vital status) will be collected by the national breast cancer screening program through linkage with the National Cancer Registry, Statistics Netherlands, and the municipal administration registration. Continuous linkage with these registries is already in place, independent from the DENSE trial, as part of routine evaluation of the national breast screening program. The information is pseudonymized before being sent to the researchers.

Table 2

Overview of MR Imaging Hardware, Contrast Medium, and Sequence Parameters

Parameter	Precontrast T1-weighted Sequence	T2-weighted Sequence	Diffusion-weighted Imaging Sequence	High-Temporal-Resolution Dynamic Contrast-enhanced Sequence	High-Spatial-Resolution Dynamic Contrast-enhanced Sequence
Acquisition voxel size (mm) (in-plane × section thickness)	0.65 × 0.65 × 2.00, 1.00 × 0.80 × 1.00, 1.00 × 1.00 × 1.00	0.90 × 0.90 × 4.00, 0.90 × 1.20 × 2.50, 1.00 × 1.33 × 2.00, 1.00 × 1.45 × 2.00, 1.00 × 1.46 × 2.00, 1.11 × 0.89 × 2.50	1.30 × 1.70 × 4.00, 1.55 × 1.55 × 4.00, 2.00 × 2.00 × 5.00, 2.25 × 2.50 × 3.00, 2.25 × 2.51 × 3.00	0.90 × 1.00 × 3.21, 0.90 × 1.00 × 3.25, 1.04 × 0.94 × 3.26, 2.58 × 2.50 × 3.00, 2.58 × 2.82 × 6.00	0.80 × 1.00 × 1.30, 0.89 × 0.92 × 1.80, 0.90 × 0.92 × 1.80, 0.90 × 1.00 × 1.30
Reconstructed voxel size (mm) (in-plane × section thickness)	0.64 × 0.64 × 1.00, 0.65 × 0.65 × 1.00, 0.94 × 0.94 × 1.00, 1.00 × 0.80 × 1.00	0.64 × 0.64 × 2.00, 0.66 × 0.66 × 2.00, 0.89 × 0.89 × 2.50, 0.90 × 0.90 × 2.50, 0.90 × 0.90 × 4.00	1.25 × 1.25 × 3.00, 1.30 × 1.70 × 4.00, 1.50 × 1.50 × 4.00, 1.55 × 1.55 × 4.00	0.90 × 0.90 × 2.50, 0.94 × 0.94 × 2.50, 0.97 × 0.97 × 1.50, 0.97 × 0.97 × 3.00, 1.18 × 1.18 × 3.00	0.80 × 0.80 × 1.00, 0.89 × 0.89 × 0.90, 1.00 × 0.80 × 1.00
Acquisition time (sec)	80–152	147–248	215–301	1	5–6
No. of precontrast acquisitions	...	...	...	1	...
No. of high-temporal-resolution postcontrast acquisitions	...	...	...	15–19	...
No. of high-spatial-resolution postcontrast acquisitions	...	...	...	...	5–6

Note.—All MR imaging examinations were performed in the axial plane with bilateral anatomic coverage, a field strength of 3.0 T, either a seven- or a 16-channel phased-array dedicated bilateral breast coil, a computer-aided diagnosis system (DynaCad, MultiView, IteraRecon, or BreVis), and a 0.1-mL dose of gadobutrol per kilogram of body weight injected at a rate of 1 mL/sec. The acquisition times for the high-temporal-resolution and high-spatial-resolution dynamic contrast-enhanced sequences were together 301–402 seconds.

Study End Points

The primary outcome is the difference in the proportion of interval cancers between the two trial arms. Secondary outcomes are the number of MR imaging screening-detected breast cancers and the proportion of false-positive MR imaging results. The positive predictive value and sensitivity of MR imaging screening will be assessed. Tumor size, stage, and grade distributions, including tumor histologic and molecular subtypes (eg, luminal A, luminal B, basal-like, and HER2), will be compared between the trial arms. The impact of MR imaging screening on quality of life and the cost-effectiveness of the new screening strategy will be assessed.

An interval cancer is defined as a breast cancer diagnosed after a negative screening examination but before the next scheduled screening examination (approximately 2 years later).

The diagnostic yield of MR imaging will be determined, with the highest BI-RADS score of each MR imaging examination as a study end point. A distinction will be made between a positive MR imaging examination (BI-RADS category 3, 4, or 5) and a positive MR imaging examination with an indication for biopsy (BI-RADS category 4 or 5). Positive predictive value (PPV) 1 is defined as the rate of histologically proven malignancy among women with a positive MR imaging examination. PPV 2 is defined as the rate of histologically proven malignancy among women with a positive MR imaging examination with an indication for biopsy. PPV 3 is defined as the rate of histologically proven malignancy among women with a positive MR imaging examination who underwent biopsy. The sensitivity of MR imaging in women with a negative result at mammography will be calculated by dividing the number of MR imaging screen-detected breast cancers by the sum of MR imaging screen-detected breast cancers plus the interval cancers.

Questionnaires on risk factors and quality of life are administered to the women in the intervention group at several points in time during the trial (Table 3). A questionnaire on health status and breast cancer risk factors is

completed at the time of recruitment, and then a follow-up questionnaire is completed each year to assess changes in health status or risk factors. The impact of MR imaging screening on quality of life will be assessed by using standardized and validated questionnaires that are filled out at several points in time during the trial (including before and after the MR imaging examination). These results will be compared with data on quality of life of the general population of Dutch women aged 50–75 years, with the assumption that the quality of life of these women equals the quality of life of the women in the control arm. The EuroQol Five-Dimensional (EQ-5D) questionnaire is a validated and frequently used questionnaire that assesses a woman's physical and psychologic health status (41). Furthermore, the Consequences of Screening in Breast Cancer (COS-BC) questionnaire is used to measure the psychosocial impact of the screening strategy being studied (42,43). In addition, the screen-specific items questionnaire is used to measure any pain, discomfort or anxiety experienced during the MR imaging examination (44). Participants in the intervention arm who are given a diagnosis of breast cancer are asked to fill out the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) and EORTC-QLQ-BR23 questionnaire to investigate the quality of life of patients with breast cancer (45,46).

Because mortality as an outcome measure requires a very lengthy follow-up and a much larger population than included here, the Microsimulation Screening Analysis, or MISCAN, computer simulation program will be used to evaluate potential mortality reductions. MISCAN is a breast cancer screening simulation model that has been specifically developed for building models for cancer screening in a dynamic population (the Dutch screening population is a dynamic population, because membership in the population is not fixed, as women are members only while they are between 50 and 75 years old and reside in the Netherlands) and

**Table 3****Questionnaire Schedule**

Time Point	Questionnaire
Recruitment	Questionnaire on health status and risk factors; COS-BC, EQ-5D questionnaires
2 Days after MR imaging examination	Screen-specific items, COS-BC, EQ-5D questionnaires
30 Days after MR imaging examination	COS-BC, EQ-5D, EORTC-C30,* EORTC-BR-23* questionnaires; questionnaire on (serious) adverse events
1 Year after recruitment <sup>†</sup>	Questionnaire on changes in health status and risk factors; COS-BC, EQ-5D questionnaires

Note.—COS-BC = Consequences of Screening-Breast Cancer, EORTC = European Organisation for Research and Treatment of Cancer, EQ-5D = EuroQol Five-Dimensional.

\* Only participants with a diagnosis of breast cancer complete this questionnaire.

<sup>†</sup> Repeated annually.

subsequently for applying these models to analyze and explain results of cancer screening trials (47–49).

MISCAN will also be used to predict costs and effects of various screening strategies, with screening performed during a period of 10 years. The costs of additional diagnostic work-up after a positive MR imaging examination (including follow-up imaging and histologic verification) will be recorded during the trial. Furthermore, data on the costs of breast cancer treatment and follow-up cancer care will be collected. In addition, participants in the intervention arm are asked to report any trial-related sickness absence (nonattendance at work) and reduced work productivity (reduced performance at work). Costs and effects will be calculated for the simulated cohort of 1 million women for a period of 10 years after the start of screening. The costs will be presented in European currency (€). The effects will be presented in terms of breast cancer mortality reduction and number of life-years gained. Cost-effectiveness ratios will be expressed as cost per life-year gained, and incremental cost-effectiveness ratios will be expressed as additional cost per additional life-year gained. For estimating quality-adjusted life-years, data on EQ-5D health state in the (general) population of Dutch women aged 50–75 years will be used as a proxy-rated quality of life in the control arm.

For safety reasons, potential (serious) adverse events are reported by the MR imaging technologist directly after the MR imaging examination. Furthermore, a questionnaire on (serious) adverse events is administered to the participants 30 days after the MR imaging examination.

**Sample Size**

The primary aim of the DENSE trial is to detect a statistically significant reduction in the interval cancer rate of the intervention arm (mammography and MR imaging) compared with the control arm (mammography alone). The following assumptions have been made for the sample size calculation. In the Netherlands, the breast cancer incidence for the age group 50–69 years with extremely dense breasts (ACR category 4) is estimated to be 8.0 per 1000 screening examinations (5,50). The sensitivity of a biennial mammographic screening program has been described to be 0.45 for women with extremely dense breasts (ACR category 4) compared with 0.82 for those with fatty breasts (ACR category 1) (51). Because MR imaging is expected not to be limited by the amount of dense tissue, the combination of mammography and MR imaging is assumed to be able to achieve a sensitivity of at least 0.82 in women with extremely dense breasts. Sensitivities used here are from a biennial screening program and therefore

are lower than what has been observed in the majority of studies, which are based on annual screening programs. Additional screening with MR imaging will then lead to a reduction in the interval cancer rate in women with extremely dense breasts, from 4.4 [(1 - 0.45) · 8] per 1000 screening examinations to 1.44 [(1 - 0.82) · 8] per 1000 screening examinations. Owing to the prerandomization design, for the sample size calculation, we have taken into account that there are women who will not participate after having been randomized. These nonparticipants will be analyzed in the intervention group according to the intention-to-treat principle. In the ACRIN 6666 trial, 57.9% of the women approached for the MR imaging substudy wanted to participate (52). One reason for not participating was the costs of the MR imaging examination or not having insurance. Without this reason, the participation rate would have been 66%. Because in our study, subjects receive financial compensation for the MR imaging examination, the expected participation rate will be 66%. In the intervention group, the expected interval cancer rate will be 1.44 per 1000 examinations in the 66% of the population that does participate and 4.4 per 1000 examinations in the 34% that does not participate. Taken together, the interval cancer rate in the intervention group is then expected to be 2.45 per 1000 examinations. With 1:4 randomization, 7237 women are needed in the intervention group (of which 4776 [66%] are expected to actually participate), and 28948 women are needed in the control arm to be able to prove a difference between 4.4 per 1000 and 2.45 per 1000 to be statistically significant (one-sided  $\alpha$  of .05, with a power of 80% for one round of screening and its subsequent interval period).

#### Data Analysis

The primary outcome is the difference in proportion of interval cancers between the two trial arms and these proportions will be compared by using a  $\chi^2$  test (or a Fisher exact test if numbers in cells are low).

A secondary outcome is the difference in mean tumor size between the two trial arms. If normally distributed, the differences in means will be tested by using the Student *t* test. If not normally distributed, medians will be estimated and differences between distributions tested with the nonparametric Mann-Whitney *U* test. Other secondary outcomes are differences in tumor stage and grade distributions, including their histologic and molecular subtypes. Differences between the trial arms will be assessed by using a  $\chi^2$  test or the Fisher exact test.

Data will be analyzed according to the intention-to-treat principle. In addition, the analysis technique described by Cuzick et al will be applied to estimate the undiluted effect of MR imaging, which is also known as the “complier average causal effect” (53,54). In this analysis, the results among compliers in the intervention arm (those who actually underwent MR imaging) will be compared with the results among potential compliers in the control arm. This analysis relies on the assumption that the compliance rate in the intervention arm equals the potential compliance rate in the control arm (54). In addition, it is assumed that merely being offered MR imaging screening has no effect on the outcome (54).

Quality-of-life results will be presented for all time points by utilizing descriptive statistical analysis. Data will be stratified according to MR imaging result (true-negative, false-negative, true-positive, and false-positive results). The cost-effectiveness of MR imaging screening will be predicted by using MISCAN, as described above.

#### Results

The first participants were randomized in December 2011. Enrollment completion is expected in 2015. The first study results (the diagnostic yield of MR imaging) are expected to be presented in 2016.

#### Discussion

In this report, we present the rationale and design of DENSE. It has been known

for some time that women with extremely dense breasts have an increased breast cancer risk (8,9) as well as lower mammographic tumor detectability (4,5). DENSE aims to validate personalization of the national breast cancer screening program by incorporating information on mammographic density through offering a more sensitive screening modality for women with extremely dense breasts (ACR category 4).

The major strength of DENSE is its parallel-group randomized controlled design. Importantly, in the United States, randomized controlled trials are difficult to conduct, because in many U.S. states, legislation is in place that requires women with dense breasts to be notified about their mammographic density (55). In several states, insurance coverage for additional screening with MR imaging or US is required.

We use a so-called single-consent prerandomization design (20) instead of a classic randomization design to prevent anxiety and self-referral-induced contamination in the control arm. This phenomenon of self-referral-induced contamination has been observed, for example, in a prostate cancer screening trial where the serum prostate-specific antigen testing rate in the control arm was approximately 60% higher than that in the general population (56). Contamination due to additional breast cancer screening in the control arm would obscure a potential difference in interval cancer rate between the trial arms.

There are also some disadvantages to the single-consent prerandomization design. The first disadvantage is that nonparticipation, which is expected to be around 34% (52), occurs after randomization. As a result, the intervention arm includes women who do not undergo a MR imaging examination and, thus, dilute the estimated effect of MR imaging in the intention-to-treat analysis, requiring a larger sample size. To determine the undiluted effect of MR imaging, data will be analyzed according to the analysis technique described by Cuzick et al (53,54). This method enables adjustment for noncompliance in the intervention arm.



For women in the control group, only data that are routinely collected by the screening organization and cancer registry are available. This includes data on interval cancer rate and tumor characteristics and limited information on breast cancer treatment, which is sufficient to answer the primary research question of DENSE. Unfortunately, information on personal and family medical history and breast cancer risk factors is not available. Furthermore, the quality of life of the participants in the control arm is unknown. Instead, the quality of life of the general population of Dutch women aged 50–75 years will be used as proxy in the cost-effectiveness analysis.

Because the DENSE trial is performed within the framework of a biennial screening program, we based our sensitivity assumptions on density-stratified results of biennial programs (50,51), which are as yet confined to screen-film instead of digital mammography, with lower program sensitivities as a consequence. From the recent literature we now know, however, that also after a negative digital mammography examination, supplementary US imaging still reveals an additional number of 2.2–7.7 breast tumors per 1000 examinations in women with breast density ACR categories of 3 or 4 (57–60). Considering this, the reduction in interval cancer rate with two to three per 1000 that we intend to find in our trial seems reasonable to expect, especially because MR imaging is much more sensitive than US (11,12,61) and because we restrict our study to women with ACR category 4 breasts, where the gain is expected to be higher than for ACR category 3 breasts.

DENSE may also provide some insight into the additional value of MR imaging as screening modality in women younger than age 50. In the Netherlands, this age group is not routinely screened, because the efficacy of mammography is not proven for them, which may be explained not only by a low breast cancer incidence but also by a high prevalence of heterogeneously dense and extremely dense

breast tissue. Therefore, if the DENSE trial proves MR imaging to be an effective additional screening method in women with extremely dense breasts, this will give important leads for similar strategies in women younger than 50 years, in whom the prevalence of dense breast tissue is higher.

At this point in time, it is too early to advocate implementation of expensive supplementary MR imaging in the general breast cancer screening population with extremely dense breasts because effectiveness, in terms of mortality reduction and quality-adjusted life-years gained, has not been examined in randomized controlled trials. The time to act is now, before breast density legislation (such as that in the United States) induces a worldwide increase in supplementary testing that, once in place, cannot be properly evaluated and will be very difficult to reverse.

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