The Tomosynthesis study in Bergen – the To-be trial

Approved by the Regional Committees for Medical and Health Research Ethics in the South East of Norway (official record number 2015/424) and registered at ClinicalTrials.gov (NCT02835625)

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Protocol synopsis –
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Study title	Digital breast tomosynthesis – the future screening tool for breast cancer?
Study phase	Data will be collected from a two year recruitment period (2016 and 2017) and for two years after the recruitment period, for estimation of interval and breast cancer in consecutive screening round
Background	Digital breast tomosynthesis (DBT) is an advancement of mammography, and has the potential to overcome limitations of standard digital mammography (DM). The use of DBT+DM roughly doubles the radiation dose compared to DM alone. As a result, synthetic 2D mammograms (SM) was developed using raw-data from the DBT acquisition to minimize the radiation burden to women. As of yet, there is insufficient evidence to draw any conclusions about the overall balance of benefits and harms of using DBT+SM in a population-based screening program.
Study aim	To investigate the potential superiority of first generation DBT+SM versus DM in an organized population-based screening program
Study setting	The breast center at Haukeland University hospital, as a part of the national screening program, BreastScreen Norway
Study design	A large-scale, parallel group, superiority RCT
Outcome measures	*Primary outcome:* Screen-detected breast cancer *Secondary outcomes:* Recalls, positive predictive value of recalls and biopsies, prognostic and predictive tumor characteristics, economical aspects *Other Outcome Measures:* Consensus, time spent on screen-reading and consensus, mammographic features, radiation doses and other early performance measures *After two years of follow up of the individual women:* Interval cancer and screen-detected breast cancer among consecutively screened women
Study population	The target group is 45 000 women aged 50-69. We expect 75% attendance rate in the program, and 90% participation rate in the trial, resulting in 30 000 women in total, 15 000 in each arm
Inclusion/exclusion criteria	Inclusion criteria: Women who attend BreastScreen Norway with a complete screening exam and signed an informed consent Exclusion criteria: Women with breast implants were not considered for participation in the trial. Women who have prior history of breast cancer or metastatic melanoma, or who report breast symptoms when attending for screening examination will be screened as usual, but excluded post-randomization.
Randomization	Fully concealed, simple randomization and 1:1 allocation ratio. The intervention will not be blinded
Procedures	Screening with two-view DBT+SM or two-view standard DM. Independent double reading of the screening mammograms, by a pool of eight breast radiologists. All cases with a positive score will be discussed at a consensus meeting where the decision of whether to recall the women for further assessment will be taken

Assessments	Women recalled will undergo further assessment, such as additional imaging and needle biopsy
Sample size calculation	In a population with an estimated screen-detected breast cancer rate of 0.60%, we calculated that with 15,000 women in each arm, we could observe an increase in prevalence from about 0.60% with DM to 0.88% with DBT, with 80% power using a two-sided significance threshold of 5%
Statistical analysis	Variables will be described and tested using chi squared tests, t-tests, one way ANOVA and Z tests. The primary outcome will be analyzed with a log-binomial regression model and presented as crude risk ratios with a 95 % confidence interval
Safety considerations	In addition to adhering to the ethical approvals obtained, an interim analysis will be performed after 1 year and published in a peer-reviewed journal to control radiation dose and selected early performance measures
Project management	Consortium: Haukeland University Hospital Cancer Registry of Norway University of Oslo The consortium appoints a Steering Committee. The project group is led by PI Solveig Hofvind.
Study sponsor	The Norwegian Research Council