


# BMJ Open Protocol for the T-REX-trial: tailored regional external beam radiotherapy in clinically node-negative breast cancer patients with 1-2 sentinel node macrometastases – an open, multicentre, randomised non-inferiority phase 3 trial

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## ABSTRACT

**Introduction** Modern systemic treatment has reduced incidence of regional recurrences and improved survival in breast cancer (BC). It is thus questionable whether regional radiotherapy (RT) is still beneficial in patients with sentinel lymph node (SLN) macrometastasis. Postoperative regional RT is associated with an increased risk of arm morbidity, pneumonitis, cardiac disease and secondary cancer. Therefore, there is a need to individualise regional RT in relation to the risk of recurrence.

**Methods and analysis** In this multicentre, prospective randomised trial, clinically node-negative patients with oestrogen receptor-positive, HER2-negative BC and 1-2 SLN macrometastases are eligible. Participants are randomly assigned to receive regional RT (standard arm) or not (intervention arm). Regional RT includes the axilla level I–III, the supraclavicular fossa and in selected patients the internal mammary nodes. Both groups receive RT to the remaining breast. Chest-wall RT after mastectomy is given in the standard arm, but in the intervention arm only in cases of widespread multifocality according to national guidelines. RT quality assurance is an integral part of the trial.

The trial aims to include 1350 patients between March 2023 and December 2028 in Sweden and Norway. Primary outcome is recurrence-free survival (RFS) at 5 years. Non-inferiority will be declared if outcome in the de-escalation arm is not >4.5 percentage units below that with regional RT, corresponding to an HR of 1.41 assuming 88% 5-year RFS with standard treatment. Secondary outcomes include locoregional recurrence, overall survival, patient-reported arm morbidity and health-related quality of life. Gene expression analysis and tumour tissue-based studies to identify prognostic and predictive markers for benefit of regional RT are included.

**Ethics and dissemination** The trial protocol is approved by the Swedish Ethics Authority (Dnr-2022-02178-01, 2022-05093-02, 2023-00826-02, 2023-03035-02). Results will be presented at scientific conferences and in peer-reviewed journals.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Prospective randomised trial, giving the highest level of scientific evidence.
- ⇒ Participation of multiple sites and countries.
- ⇒ The trial includes breast cancer patients with oestrogen receptor (ER)-positive, HER2-negative disease and 1-2 sentinel node macrometastases.
- ⇒ Prognostic and predictive markers will be investigated through tissue-based gene assays.
- ⇒ Limitation—ER-negative, HER2-positive and/or T3-4 tumours not included.

**Trial registration number** NCT05634889.

## INTRODUCTION

Each year approximately 8000 Swedish, 4000 Norwegian and 5000 Finnish women are diagnosed with breast cancer (BC). Standard treatment for early BC is surgery combined with systemic therapy and radiotherapy (RT), which today commonly includes regional lymph nodes in case of lymph node metastases. Earlier BC trials have shown regional RT to approve prognosis for women with nodal disease on a group level.<sup>1 2</sup> In the EORTC 22922/10925 trial there was a reduction in BC-mortality with regional RT after 15-year follow-up, and the MA.20 trial shows a reduction in BC-recurrences after 10 years.<sup>3 4</sup> However, modern systemic therapy has significantly improved survival and decreased the incidence of locoregional recurrences. Regional recurrences are therefore today rare events,<sup>5–9</sup> and it is being questioned whether regional RT still have the same benefit for low-risk patients with limited nodal disease.



Current treatment recommendations on regional RT differ between countries and sites, both regarding included lymph node levels (axilla level I–III, supraclavicular and/or internal mammary nodes (IMN)) and patient selection. Regional RT is associated with a risk of complications such as arm morbidity, skin irritation, pneumonitis, cardiac disease, second cancers (lung cancer, angiosarcoma, oesophageal cancer) and hypothyroidism.<sup>10–15</sup> RT also significantly deteriorates surgical and patient-reported outcomes of breast reconstruction.<sup>16 17</sup> There is therefore a need for modern data on risks and benefits associated with regional RT, thus providing an opportunity to customise its use in relation to the individual risk of recurrence.

The ACOSOG Z0011 trial randomised patients with T1–2 invasive BC and 1–2 sentinel lymph node (SLN) metastases, treated by breast-conserving surgery (BCS) and whole-breast RT, to axillary lymph node dissection (ALND) or no further axillary treatment.<sup>18</sup> The axillary recurrence rate was low, and there was no significant survival difference between the randomisation groups after 9 years of follow-up. In a retrospective analysis on 228 available RT plans (29%), out-of-protocol regional RT had been given to 19% of patients, and in an additional ~40%, breast RT included high tangential fields covering large parts of axillary levels I–II, that is, 50%–90% of levels I–II received 95% of the prescribed dose.<sup>19</sup> It is therefore questionable whether ACOSOG Z0011 can guide clinical practice regarding the safe omission of ALND in patients with 1–2 SLN macrometastases without the addition of regional RT.

The AMAROS trial, on the other hand, included patients with T1–2 invasive BC and 1–2 SLN metastases, and randomised between ALND or regional RT. RT included all levels of the axilla and the medial supraclavicular nodes. No significant differences in survival or recurrence rate between the randomisation groups have been reported after 10 years of follow-up.<sup>15 20</sup> Both ALND and axillary RT provided equally excellent locoregional control. While lymphoedema was more commonly seen in the ALND-arm, the group receiving axillary RT had a higher incidence of difficulties in moving the arm.<sup>8</sup>

Additional trials indicating the feasibility to de-escalate regional treatment in BC are IBCSG 23–01,<sup>21</sup> OTOASOR,<sup>5</sup> OPTIMAL,<sup>6</sup> RAPCHEM,<sup>9</sup> NSABP-04<sup>22</sup> and the SINODAR-ONE trial.<sup>7</sup> Results are also awaited from the Swedish SENOMAC-trial.<sup>23 24</sup> Collectively, these trials have introduced omission of ALND as an option in patients with limited axillary lymph node involvement. It is, however, still unclear whether regional RT to the undissected axilla, supraclavicular nodes and IMN need to be part of locoregional treatment in these patients.

Currently, there is one ongoing and one completed, but not yet reported, randomised trial addressing the therapeutic value of regional RT in addition to SLN biopsy in clinically node-negative (cN0) patients with limited axillary involvement. In the POSNOC trial, patients with early BC and 1–2 SLN macrometastases are randomised

between one modality of axillary treatment (ALND or regional RT) and surveillance only. In the MA.39 trial, on the other hand, women with low-risk BC (oestrogen receptor (ER) positive, HER2-negative, OncotypeDX score <18) are randomised after SLN biopsy or ALND between regional RT and no regional RT; 1–3 macrometastases are allowed after ALND and 1–2 after SLN biopsy alone.

In order to change international guidelines, however, additional data are needed which compare the currently most common treatments, that is, SLN biopsy followed by regional RT or SLN biopsy alone, as in the planned T-REX trial. In addition, the translational protocol of the T-REX trial aims to decipher the prognostic and predictive role of tumour biology and gene expression analysis for their potential integration into future adjuvant RT individualisation.<sup>25</sup>

### Hypothesis

Refraining from regional RT in cN0 BC patients with 1–2 sentinel node macrometastases and T1–2 tumours, ER-positive and HER2-negative disease does not worsen 5-year recurrence-free survival (RFS).

Refraining from regional RT reduces arm morbidity and late RT side effects such as heart disease and non-BC malignancies (lung cancer, angiosarcoma), and potentially improves short-term and long-term health-related quality of life (HRQoL).

Genomic classifiers can prognosticate locoregional recurrences and predict benefit from regional RT, which can be used to guide future individualised adjuvant regional RT.

## METHODS AND ANALYSIS

### Overall trial design

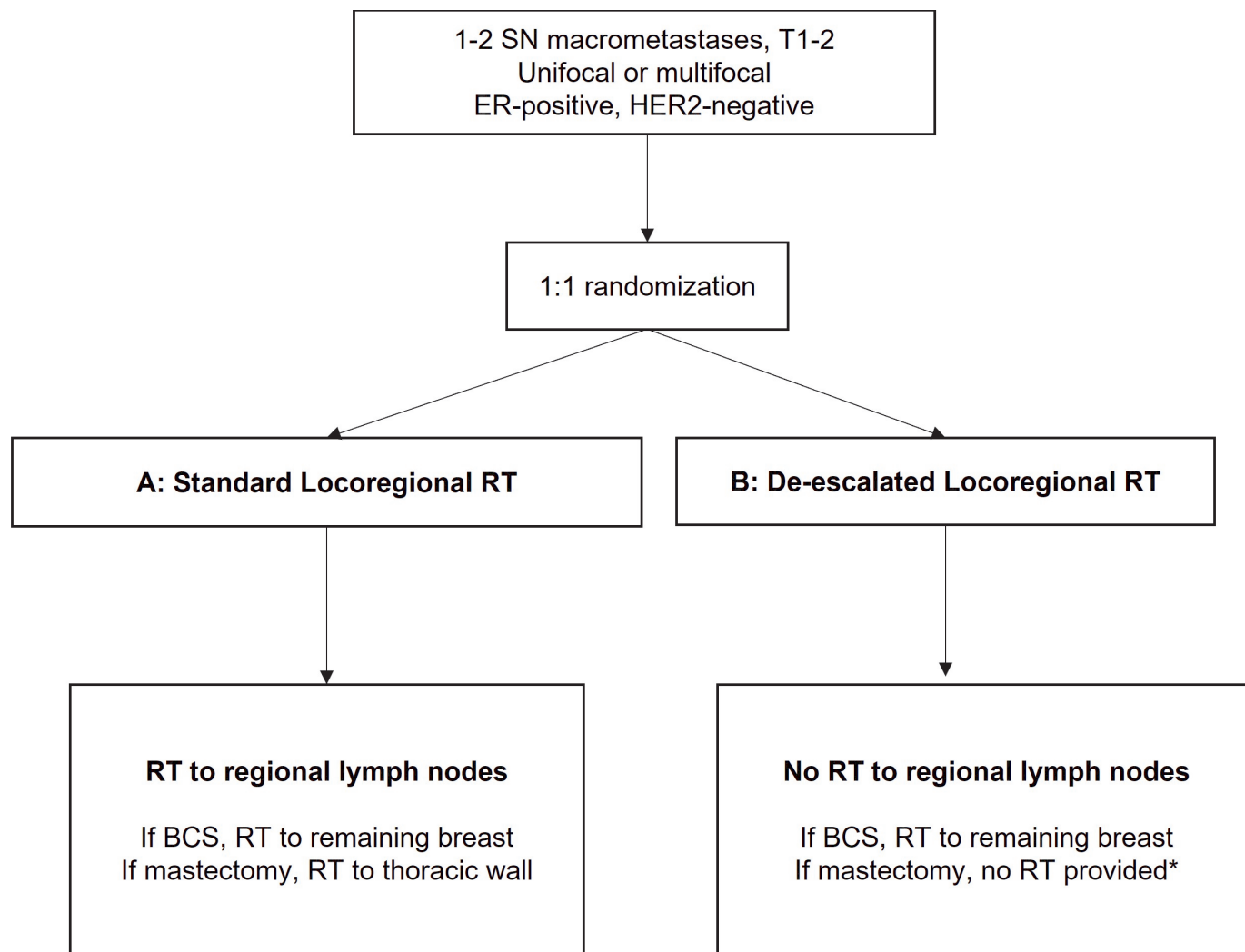
T-REX is a prospective, multicentre, open phase 3 trial (figure 1). cN0 BC patients with 1–2 SLN macrometastases and an ER-positive, HER2-negative T1–2 tumour receiving primary surgery (no neoadjuvant systemic treatment) are randomised to standard regional RT versus no regional RT. All patients will receive RT to the remaining breast after breast conserving surgery. Mastectomy patients in the intervention arm will not receive any RT, with the exception if chest wall RT is indicated due to tumour multifocality according to national guidelines.

### Arm A

Regional RT (standard): RT to the remaining breast after BCS or chest wall after mastectomy, axillary lymph nodes (levels I–III) and supraclavicular lymph nodes (level IV). IMN are included in the target volume according to national guidelines.

### Arm B

No regional RT, that is, no lymph node levels included in the target volume. RT is given to the remaining breast after BCS. No chest wall irradiation after mastectomy.



**Figure 1** Trial design. \*Exception - chest wall irradiation in the intervention arm is permitted in cases of extensive multifocality, as recommended by national guidelines. BCS, breast-conserving surgery; ER, oestrogen receptor; RT, radiotherapy; SN, sentinel node.

However, an exception is that chest wall irradiation is permitted in cases of extensive multifocality, as recommended by national guidelines.

### Trial population

After surgery, cN0 BC patients with T1-2, ER-positive, HER2-negative tumours and 1-2 SLN macrometastases are screened for eligibility. All histological tumour subtypes are eligible, and both tumour multifocality and additional SLN micrometastases are allowed. Only gross but not microscopic extracapsular extension excludes candidates from the trial. Patients who have undergone ALND or have received neoadjuvant systemic treatment prior to surgery are ineligible for the trial. Inclusion and exclusion criteria are shown in [table 1](#).

Patients are screened for eligibility within 4–5 weeks after surgery. Trial information and invitation to participate will be given by a physician at a postoperative visit at the department of surgery or oncology. The overall trial procedure is shown in [figure 2](#).

After confirmation of eligibility and written informed consent (online supplemental file 1), patients are randomised 1:1 between treatment arms using a permuted block technique. Allocation is stratified by trial site and breast surgery (BCS vs mastectomy). Participation in T-REX should not affect or change decisions on systemic adjuvant treatment. Hence, systemic adjuvant treatment should be planned and documented before randomisation according to best standard of care, taking age and comorbidity into consideration. Furthermore, it should be confirmed that the patient is willing and able to adhere to such recommended systemic therapy before inclusion in T-REX.

Locoregional RT is given 5 days per week with 15 fractions of 2.67 Gy to a total target dose of 40.05 Gy. The same fractionation is used for whole-breast RT. However, in women >50 years who shall receive whole-breast RT without a tumour bed boost, and without inclusion of nodal fields, an alternative treatment scheme may be 5 fractions of 5.2 Gy to a total target dose of 26.0 Gy. In

**Table 1** Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> <li>1. Primary unifocal or multifocal invasive breast cancer T1-T2</li> <li>2. Clinically N0</li> <li>3. Macrometastasis (&gt;2 mm) in 1-2 lymph nodes at sentinel node biopsy</li> <li>4. Oral and written consent</li> <li>5. Age ≥18 years</li> <li>6. Tumour-free resection margins (no tumour on ink)</li> <li>7. Primary tumour ER-positive, HER2-negative</li> </ol>	<ol style="list-style-type: none"> <li>1. Regional or distant metastases outside the ipsilateral axilla</li> <li>2. Previous RT towards the planned target area, that is, the ipsilateral chest/lymph nodes</li> <li>3. Neoadjuvant systemic therapy</li> <li>4. Axillary lymph node dissection or other previous axillary surgery on the affected side</li> <li>5. History of invasive breast cancer</li> <li>6. Pregnancy</li> <li>7. Bilateral invasive breast cancer</li> <li>8. Contraindication for radiotherapy or systemic treatment, if indicated. Hence endocrine treatment, chemotherapy and/or targeted therapy should at inclusion be planned to be given according to standard of care, taking age and comorbidity into consideration</li> <li>9. Inability to absorb or understand the contents of the informed consent form; for example, through disability, insufficient language skills or dementia</li> <li>10. Other invasive cancer within 5 years prior to breast cancer diagnosis</li> </ol>

ER, oestrogen receptor; RT, radiotherapy.

accordance with the Fast Forward trial and Swedish National Guidelines.<sup>26 27</sup> Tumour bed boost, IMN-RT and chest wall RT due to multifocality is given according to national guidelines.

## Outcomes

### Primary outcome

RFS at 5 years. RFS is measured from the date of randomisation until the date of first local recurrence, regional recurrence, distant recurrence or death by any course.

### Secondary outcomes

Oncological outcomes:

- ▶ Locoregional recurrence.
- ▶ Overall survival, distant RFS.
- ▶ Contralateral BC.

Treatment-related outcomes:

- ▶ Arm morbidity at 1, 3 and 5 years assessed through the 'Lymphedema Functioning, Disability and Health Questionnaire' developed by Devoogdt in 2011.
- ▶ Quality of life assessed through EORTC questionnaires QLQ-30 and BR-23 at 1, 3 and 5 years. In

addition, sense of coherence will be evaluated at baseline through the SOC-13 questionnaire.

- ▶ Cardiac morbidity and incidence of non-breast malignancies (such as lung cancer and angiosarcoma) will be assessed using register data.

### Tissue collection and analysis

When signing the informed consent form, participants will explicitly grant or abstain from permission for tissue collection, handling and biobanking/storage, and the use of such tissue in gene expression assays and translational analyses. For patients who agree to this, tissue from the primary tumour, surrounding stromal tissues and lymph node metastases will be collected and stored at a trial biobank in Gothenburg, Sahlgrenska University Hospital. Tissue samples from any recurrences during follow-up will be also collected.

Collected tumour tissues will be used for molecular analyses including gene expression signatures in order to identify genomic classifiers which can prognosticate locoregional recurrences and predict benefit from regional RT.



**Figure 2** Trial procedure. BCS, breast-conserving surgery; MRM mastectomy; SN, sentinel node.

**Table 2** Flow chart of follow-up

	Screening	Baseline	End of RT	1 year*	3 years*	5 years*	10 years*
	After surgery	Before start of RT	±2 months	±2 months of randomisation date			
Verify eligibility	X						
Obtain informed consent							
Randomisation	X						
Register patient and tumour characteristics†		X					
Register breast reconstruction data		X	X	X	X	X	X
Register adjuvant systemic therapy‡			X	X	X	X	X
Register detailed RT data			X				
Register recurrences and death				X	X	X	X
Arm morbidity questionnaire (Lymph-ICF)		X		X	X	X	
HRQoL questionnaires (EORTC QLQ-C-30 and BR-23)		X		X	X	X	
Sense of coherence questionnaire (SOC-13)		X					
Tumour tissue sent to biobank		X					

\*All relevant information may be retrieved by physical visits or telephone contact with the participant, and/or through review of medical chart according to each site's routine.  
 †Including demography, height, weight, waist and hip circumference, preoperative breast size, smoking history, current nicotine use and biomarker data.  
 ‡Adjuvant systemic therapy should be given according to standard of care.  
 Lymph-ICF, Lymphedema Functioning, Disability and Health Questionnaire; RT, radiotherapy.

### Follow-up and quality assurance

Patients will be followed prospectively according to each site's clinical routine and participating countries' national guidelines. That is, no specific follow-up modality or schedule is postulated. Assessment of disease recurrence and questionnaire results for patient-reported arm morbidity and HRQoL will be registered in the electronic case report form (eCRF) at baseline, year 1, 3, 5 and 10 (table 2).

The trial will be monitored by independent monitors to ensure that it is carried out according to the protocol and that data is collected, documented and reported according to good clinical practice and applicable ethical, legal and regulatory requirements.

Further, an RT quality assurance (QA) programme is an integral part of the trial. Before entering, each centre will need to submit a benchmark delineation case for a left sided locoregional treatment including IMN. Treatment planning will be reviewed in conjunction with the RT for at least three patients from each centre: the first recruited left sided breast patients with breast only, locoregional without IMN and locoregional with IMN, respectively.

RT-related data are reported in the eCRF by each centre for all patients. Data in DICOM format (CT images, dose plan, dose distribution and structures) as well as a treatment report from the oncology information system is

collected by the QA centre for all Swedish patients and potentially for selected centres in other participating countries. This will be used to on a group level investigate dose to individual lymph node levels in the respective treatment arms. For patients with locoregional recurrence, a detailed described of its position in relation to previous RT-fields and dose will be given.

### Time plan

The trial has started inclusion March 2023. First publication regarding QoL is planned for 2025–2026. End of inclusion is estimated to 2028 and publication of the primary endpoint 5-year RFS to 2033.

### Participating countries and sites

The trial will initially include patients in Sweden and Norway, with the plan to extend inclusion also to Finland. In addition, the trial is open for adding further countries in the future. A full list of currently recruiting sites can be retrieved from the clinical trials office (cto.hematologi-onkologi.sus@skane.se).

### Patient and public involvement

Patient representative Jaana Korkeamäki of the Swedish Breast Cancer Association's steering committee is member of the T-REX trial steering committee. She has

taken active part in preparing the trial protocol and the informed consent form and will be updated and involved in every stage of the trial.

### Statistics, power calculations and data analysis plan

The aim of T-REX is to establish that the intervention (no regional RT), is statistically non-inferior to standard of care (regional RT) for the primary endpoint RFS. Clinical non-inferiority is defined as a 5-year RFS not worsened by more than 4.5 percentage units when refraining from regional RT. The non-inferiority margin was chosen with consideration of similar ongoing trials on axillary treatment in BC, for example, the Alliance trial and NSABP B-51 (non-inferiority margins 6 versus 4.6 percentage units, respectively, NCT01901094, NCT01872975).

Calculations are based on the assumptions of constant incidence of RFS events and a 5-year RFS of 88.0% in the standard arm, corresponding to the estimated 5-year RFS of the SENOMAC trial ([www.senomac.se](http://www.senomac.se), currently unpublished data).

Assuming uniform inclusion during 5 years plus 5 years follow-up after completed inclusion, a total of 1221 patients need to be included in the trial to have 80% power to show that the 5-year RFS is not worsened by more than 4.5 percentage units (ie, a 5-year RFS of 83.5% in the intervention group compared with 88.0% in the standard group), using a one-sided test at the  $\alpha$  level 5%. The 1221 patients should correspond to 213 events contributing to RFS. Drop-outs will not be replaced by a new randomisation. Hence, to allow for a drop-out of 10%, 1350 patients will be included. However, with the addition of more sites the trial opens for the possibility to include up to 1800 patients, which would yield statistical power for the primary endpoint to be reached already after 3 years of follow-up.

The primary analysis will be an unadjusted Cox regression with stratification for site based on the per-protocol population. However, primary outcome will also be evaluated in the intention to treat population. Since treatment is allocated randomly, adjustment for confounding will not be applied. Proportional hazards over the follow-up time will be assumed. Under the assumptions specified in the power calculation and exponentially distributed survival times, a non-inferiority margin of 4.5 percentage units translates to an upper limit of a one-sided 95% CI of 1.41 for the RFS-HR for regional RT versus no regional RT. Non-inferiority can be claimed if the upper limit does not exceed this value.

Homogeneity of treatment effect, intervention versus standard of care, will be analysed for subgroups based on age, BC stage, etc, and presented as forest plots. A Kaplan-Meier graph will be used to visualise the effect of treatment on RFS. Extensive monitoring should keep the rate of missing values for key variables low. Hence imputation techniques will not be applied. Patients who withdraw their informed consent or are lost to follow-up will be censored from the trial at this point.

An independent data safety monitoring committee will carry out a safety analysis 3 years after randomisation of the first patient, or when 500 patients have been included, whichever comes first. This is to assess recruitment rates, RFS events per group, and to make sure that patients in the intervention group do not appear to fare significantly worse than those in the standard group. The committee may recommend prematurely terminating the trial if a significant benefit in favour of standard of care for RFS is shown, such that the HR for intervention versus standard of care significantly ( $p < 0.001$ ) exceeds 1, or if the recruitment is so low that the necessary number of events is unlikely to be reached.

### Ethics and safety considerations

Based on older studies, an increased risk of recurrence among individual patients who do not undergo regional RT after ALND cannot be ruled out. However, several modern-era de-escalation trials have not shown any significant difference in survival or recurrences between trial arms. In addition, newer studies report generally improved survival and lower rates of locoregional recurrences compared with older ones, presumably due to improved systemic therapy, although a direct effect of RT cannot be excluded. In T-REX, eligibility is based on a low-risk profile regarding locoregional recurrence according to validated clinical markers such as tumour size, number of lymph nodes involved, ER and HER2 status.<sup>28</sup> Abstaining from regional RT for part of the patient population eligible for T-REX is already clinical routine in a number of countries. All study participants will be monitored for recurrences and receive treatment as indicated. In addition, a safety analysis will be performed as described earlier.

The possible risks of abstaining from RT must be weighed against significant benefits. BC patients have a long expected survival, and it is of utmost importance to keep long-term side effects to a minimum. Furthermore, RT is associated with a risk of acute and late side effects, such as skin toxicity, pneumonitis, arm morbidity, cardiac disease, lung cancer, angiosarcoma and hypothyroidism.<sup>10–14</sup> The possibility to abstain from regional RT in patients with a low risk of regional recurrence would reduce side effects and lead to reduced morbidity, improved working ability and possibly increased HRQoL. Mastectomy patients would be spared 3 weeks daily visits to the RT department, and in patients receiving breast reconstruction, the significant risk of short-term and long-term complications and poor cosmesis associated with RT would be reduced. For patients operated with BCS, not adding regional RT to whole-breast irradiation would reduce treatment time from 3 weeks to 1 week if giving 5.2 Gy  $\times$  5 fractions to a total dose of 26 Gy in accordance to the Fast Forward trial.<sup>26</sup> Finally, refraining from regional RT will save healthcare resources due to reduced work load in the hospitals.

The current benefit of regional RT in patients with limited SLN macrometastasis is unclear, and treatment

guidelines differ between countries and sites. There is therefore a need to explore this question through a randomised trial such as T-REX. In addition, gene expression analyses will be performed in order to determine their value in relation to prediction of locoregional recurrence, and for decision on adjuvant RT in the future.

This trial protocol (version 1.2, 5 May 2023) has been approved by the Swedish Ethics Authority (Dnr 2022-02178-01, 2022-05093-02, 2023-00826-02 and 2023-03035-02), and ethical permission is currently being applied for in Norway (decision expected September 2023). Furthermore, we intend to extend the trial to centres in Finland. The trial will be carried out in accordance with The Code of Ethics of the World Medical Association. All patients will sign an informed consent form before randomisation and will be free to withdraw from the trial at any time. The academic study steering committee will have ultimate authority over study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication. This will not be affected by current or possible future funders or industrial collaborators in translational projects.

### Dissemination plan

Results from the primary and secondary endpoints are planned to be published in scientific peer-reviewed journals, and at scientific conferences. Important protocol modifications will immediately be communicated to relevant parties (eg, investigators, trial participants, trial registries, regulators, etc).

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**Contributors** All authors have made a substantial contribution to the conception and/or design of the work; and/or the acquisition, analysis, or interpretation of data for the work. All authors have participated in drafting the work and reviewing it critically. All authors have approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Their individual roles and contributions are specified here. SA: primary investigator of the trial; planned the trial and drafted the study protocol; main author of manuscript and study protocol. JdB: part of the trial steering committee; planned the trial and drafted the study protocol; participated in drafting the manuscript and reviewing it critically. PK: part of the trial steering committee; planned the trial and drafted the study protocol; participated in drafting the manuscript and reviewing it critically. DL: part of the trial steering committee; planned the trial and drafted the study protocol; participated in drafting the manuscript and reviewing it critically. LR:

part of the trial steering committee; planned the trial and drafted the study protocol; participated in drafting the manuscript and reviewing it critically. IM: part of the trial steering committee; planned the trial and drafted the study protocol; primary investigator for Norway; participated in drafting the manuscript and reviewing it critically. EW: part of the adjunct steering committee; responsible for writing the radiotherapy appendix in the study protocol and planning of radiotherapy quality control; participated in drafting the manuscript and reviewing it critically. JV: part of the Norwegian trial steering committee; responsible medical physicist for Norway; participated in writing the radiotherapy appendix in the study protocol and planning radiotherapy quality control; participated in drafting the manuscript and reviewing it critically. P-OB: part of the adjunct steering committee; trial statistician, responsible for statistical calculations in the study protocol; planned the trial and drafted the study protocol; participated in drafting the manuscript and reviewing it critically. EH: part of the adjunct steering committee; trial statistician, responsible for statistical calculations in the study protocol; participated in drafting the manuscript and reviewing it critically. HS: part of the adjunct steering committee; responsible for health-related quality of life assessments and questionnaires regarding arm morbidity specified in the study protocol; participated in drafting the manuscript and reviewing it critically.

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**Competing interests** SA has received honorary for lecturing for Astra Zeneca. LR has received honorary for lecturing from Onkologisk tidskrift, Denmark. PK and EH has contract with PFS Genomics/Exact Sciences regarding genomic profiling, are coinventor on patent applications, and have a contract with Prelude Dx.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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