Is axillary lymph node dissection indicated in SN positive breast cancer?

The SENOMAC trial

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The SENOMAC trial

Omission of axillary clearance in breast cancer patients with sentinel node macrometastasis: A randomised prospective trial.

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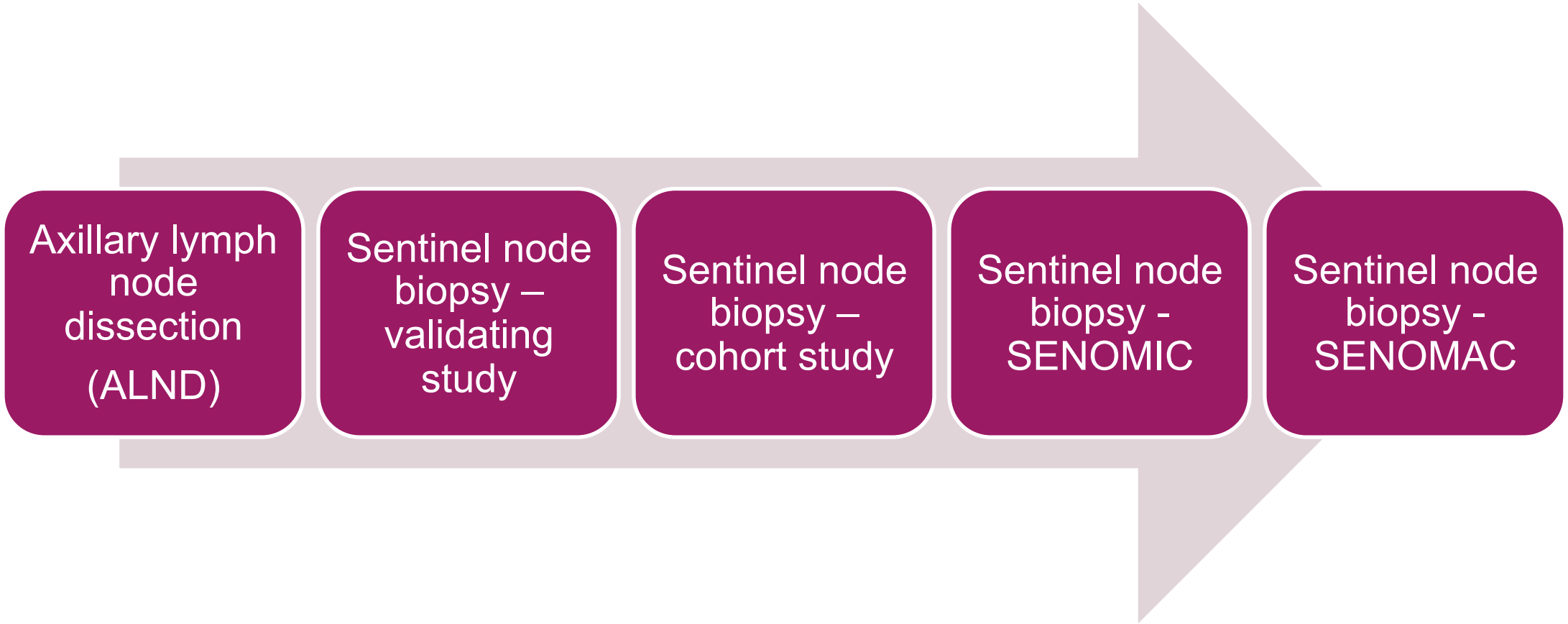
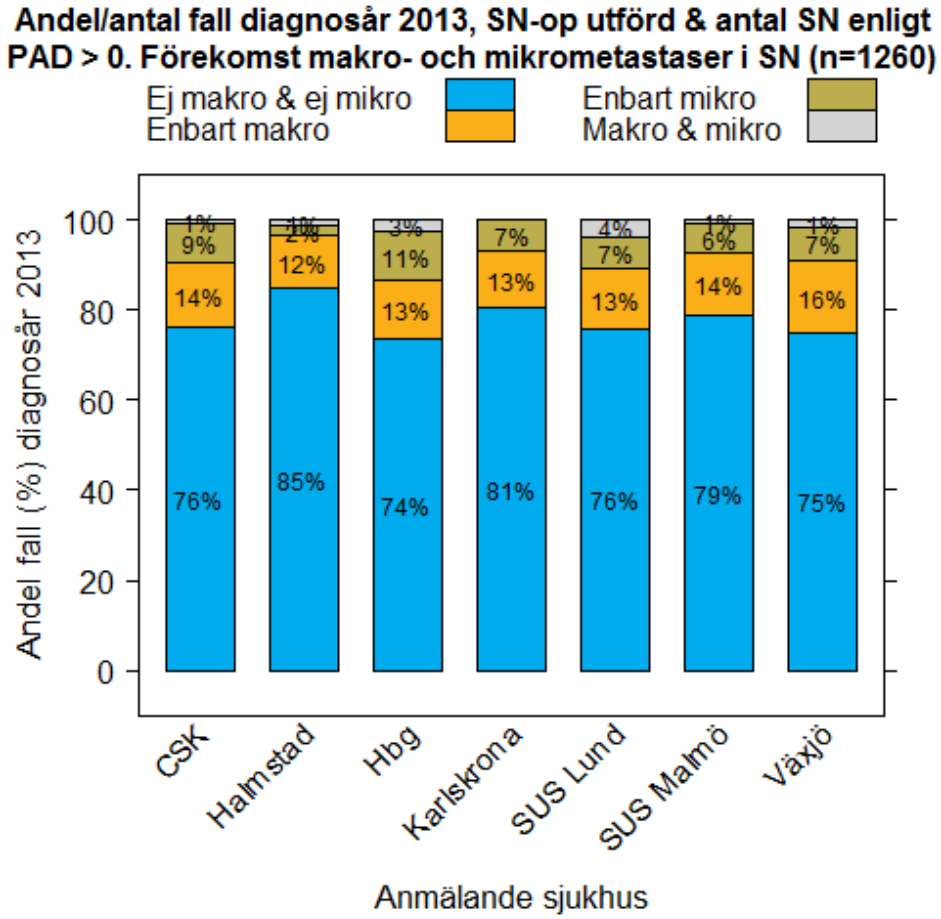
The development of axillary staging in Sweden



Classification of axillary lymph node metastasis (TNM)

- **N0** = benign
- **N0(itc)** = isolated tumor cells; 0,2 mm or less in size/ < 200 tumor cells = **benign**
- **N1mic** = metastases >0,2 mm < 2 mm; > 200 tumor cells (**micrometastasis**)
- **N1mac** = metastases > 2 mm (**macrometastasis**)

Metastasis in SLN (23%) excluding patients with upfront ALND



Macrometastasis 14%
Macro/micromet 2%
Micrometastasis 7%

Overall N+: 23%

The consequence of leaving metastatic lymph nodes in the axilla

- **Benign SN:** The sentinel node biopsy technique accepts **a false negative rate <10%.** Current data shows a low risk for axillary recurrence when omitting ALND in patients with a benign SN (10 years follow-up: 1,6 % axillary recurrences) indicating that it is safe to leave some nodes behind.

- **NSABP B-04**: 3 randomised arms: mastectomy + ALND *vs* mastectomy + locoregional RT *vs* mastectomy without any difference in 5 year OS

For most patients with macrometastasis in the SN

this is the only metastases

Node positive patients by tumour size

N+ (%)	< 5mm	6-10 mm	11-20 mm	21-30 mm	> 31 mm
Screening	6	7	14	23	37
Symtomatisk	0	2	16	37	32
Alla	5	5	15	30	33

INCA-utdrag RCC Syd 161008

Node positivity for different sizes and detection mode

	Size	
	1–10 mm n = 1 135	11–15 mm n = 1 190
Screen detected (%)	7	18
Clinical detected (%)	14	31
All inv. Cancers (%)	11	24

n = 2 325.

Arnesson LG & Ahlgren J, Acta Oncol 2000

ESMO Guidelines (Annals of Oncology 2015)

- SLNB rather than full axillary nodal clearance, is now the standard of care, unless axillary node involvement is proven [II, A].

- Patients with isolated tumour cells (<0.2 mm) in the sentinel node and patients with limited involvement of the sentinel lymph nodes undergoing tangential breast irradiation may not need to have any further axillary procedure [II, B].

Is axillary lymph node dissection indicated in all patients with SN positive breast cancer?

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

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Context Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Sentinel node macro/micrometastasis

- **ACOSOG Z0011**:

  891 patienter with 1-2 metastatic SN

  sentinel node biopsy + ALND *vs* **sentinel node biopsy**

No evidence of inferior outcome for patients in the sentinel node biopsy ONLY arm

→ 41% of the patients had only micrometastases
→ Breast-conserving surgery ONLY including postoperative radiation
→ Slow accrual (115 centres), target population (1900) was not acheived
→ 98 pat with pNx; 33 pat with N0; 15 pat with> 2 pos nodes in the SNB only arm
→ In the SNB only arm 371 patients could be analyzed per protocol including 45% with micrometastases

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Viviana Galimberti, Bernard F Cole, Stefano Zurrida, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23–01 investigators

Summary

Background For patients with breast cancer and metastases in the sentinel nodes, axillary dissection has been standard treatment. However, for patients with limited sentinel-node involvement, axillary dissection might be overtreatment. We designed IBCSG trial 23–01 to determine whether no axillary dissection was non-inferior to axillary dissection in patients with one or more micrometastatic (≤2 mm) sentinel nodes and tumour of maximum 5 cm.

Methods In this multicentre, randomised, non-inferiority, phase 3 trial, patients were eligible if they had clinically non-palpable axillary lymph node(s) and a primary tumour of 5 cm or less and who, after sentinel-node biopsy, had one or more micrometastatic (≤2 mm) sentinel lymph nodes with no extracapsular extension. Patients were randomly

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This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on

Sentinel node micrometastasis

- **IBCSG 23-01**:

  931 patients with sentinel node micrometastasis

  sentinel node biopsi + ALND *vs* **sentinel node biopsy only**

No difference in mortality or recurrence according to the allocated arm

- 70 % av micromet ≤ 1 mm
- 95-96 % only 1 positive SN
- 13 % non-SN metastaser i axillgruppen
- **91 % breast-conserving surgery**

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial

Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Luigi Cataliotti, A Helen Westenberg, Jean H G Klinkenbijl, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Grard A P Nieuwenhuijzen, Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Marko Snoj, Nigel J Bundred, Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Bogaerts, Emiel J T Rutgers

Summary

Background If treatment of the axilla is indicated in patients with breast cancer who have a positive sentinel node, axillary lymph node dissection is the present standard. Although axillary lymph node dissection provides excellent regional control, it is associated with harmful side-effects. We aimed to assess whether axillary radiotherapy provides comparable regional control with fewer side-effects.

Methods Patients with T1–2 primary breast cancer and no palpable lymphadenopathy were enrolled in the randomised, multicentre, open-label, phase 3 non-inferiority EORTC 10981-22023 AMAROS trial. Patients were randomly assigned (1:1) by a computer-generated allocation schedule to receive either axillary lymph node dissection or axillary radiotherapy in case of a positive sentinel node, stratified by institution. The primary endpoint was non-inferiority of

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See Comment page 1280

Department of Surgical Oncology (M Donker MD, M E Straver MD, Prof E J T Rutgers MD),

Why another randomised trial in relation to the extent of axillary surgery?

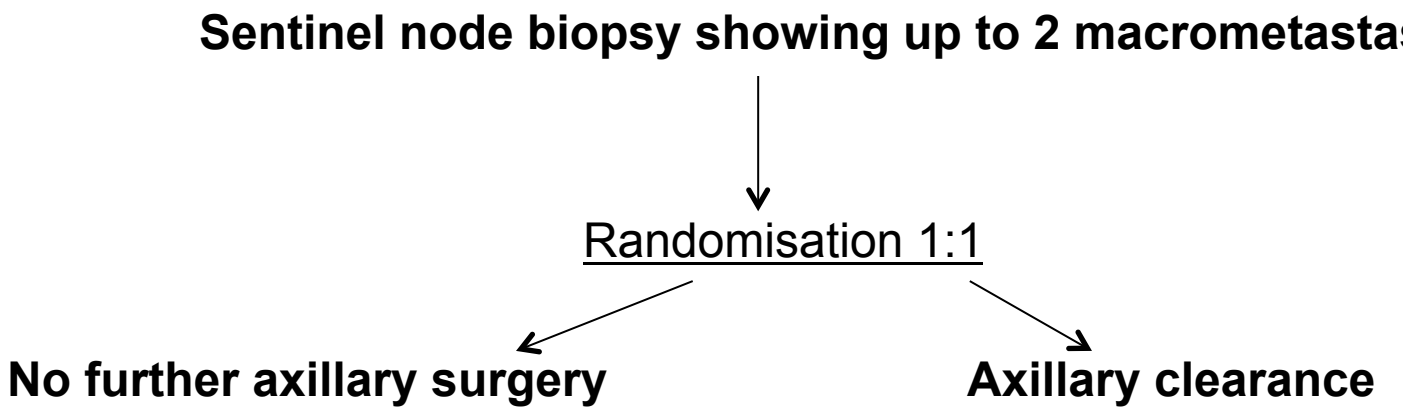
- Is the evidence enough for patients undergoing breast-conserving surgery?
  → Updated guidelines after inclusion of patients in the Z0011 (ending 2004)

- Is there any evidence for patients undergoing mastectomy with a positiv SN in relation to completion ALND?

- A call for
  → A comprehensive cohort including all breast cancer patients irrespective of breast surgery
  → A nationwide approach for handling patients with positive SN

The SENOMAC trial

Omission of axillary clearance in breast cancer patients with sentinel node **macrometastasis**: A randomised trial.



NCT 02240472 (www.clinicaltrials.gov)

www.senomac.se

the SENOMAC trial

Karolinska Institutet

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the SENOMAC trial

Omission of Axillary Clearance in Breast Cancer Patients With Sentinel Node Macrometastases: a Randomized Trial

Since the introduction of sentinel node biopsy in breast cancer, it has become clear that its use is reliable and reproducible. Today, it is clinical routine to not remove further lymph nodes from the axilla (arm pit) in case the sentinel node (which is the first lymph node/s reached by lymphatic flow from the breast) is free of tumor deposits. It is also routine to leave remaining lymph nodes behind in case the sentinel node contains a minimal cluster of tumor cells, called isolated tumor cells (formerly submicrometastasis). Even in slightly larger tumor deposits, so called micrometastasis (up to 2 mm in size), it has been shown that a completion axillary clearance (removal of further lymph nodes from the arm pit) does not contribute to a better survival. Data from a randomized study indicate that it seems safe to omit axillary clearance even if the sentinel node biopsy shows up to 2 nodes with tumor deposits over 2 mm in size (macrometastasis). These studies have changed clinical practice in many countries, however, it is still debated whether it is safe to omit axillary clearance in the case of sentinel node macrometastasis due to under-recruitment in the aforementioned study. The rationale for omitting extensive axillary surgery is the avoidance of postoperative morbidity such as arm lymphedema, loss of sensation, pain and swelling.

Steering committees

- Jana de Boniface
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- John Öhrvik, Stockholm
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- Kliniska prövningsenheten, Clinical Trial Office, Karolinska
- Good Clinical Practice

Endpoints

- **Breast cancer-specific survival**

- Overall survival
- Disease-free survival
- Axillary recurrence

- *Arm morbidity*
- *Quality of life*
- *Health economy/costs*

→ EORTC B-23
EORTC QLQ-C30
Lymph-ICF
EQ5D

Hypothesis

- Non-inferiority design: The omission of axillary clearance in the case of 1-2 SNB macrometastases does not decrease 5-year breast cancer-specific survival by more than 2.5%

- The omission of axillary clearance improves quality of life and decreases arm morbidity.

→ ***3500 patients overall***

Inclusion criteria

- Primary invasive breast cancer **T1-T3**
- No palpable lymph node metastases preop
- Preop ultrasound of the axilla performed
- 1-2 SN with macrometastasis
- Breast-conserving surgery or mastectomy +/- reconstruction
- Age ≥ 18 years both genders
- Informed consent

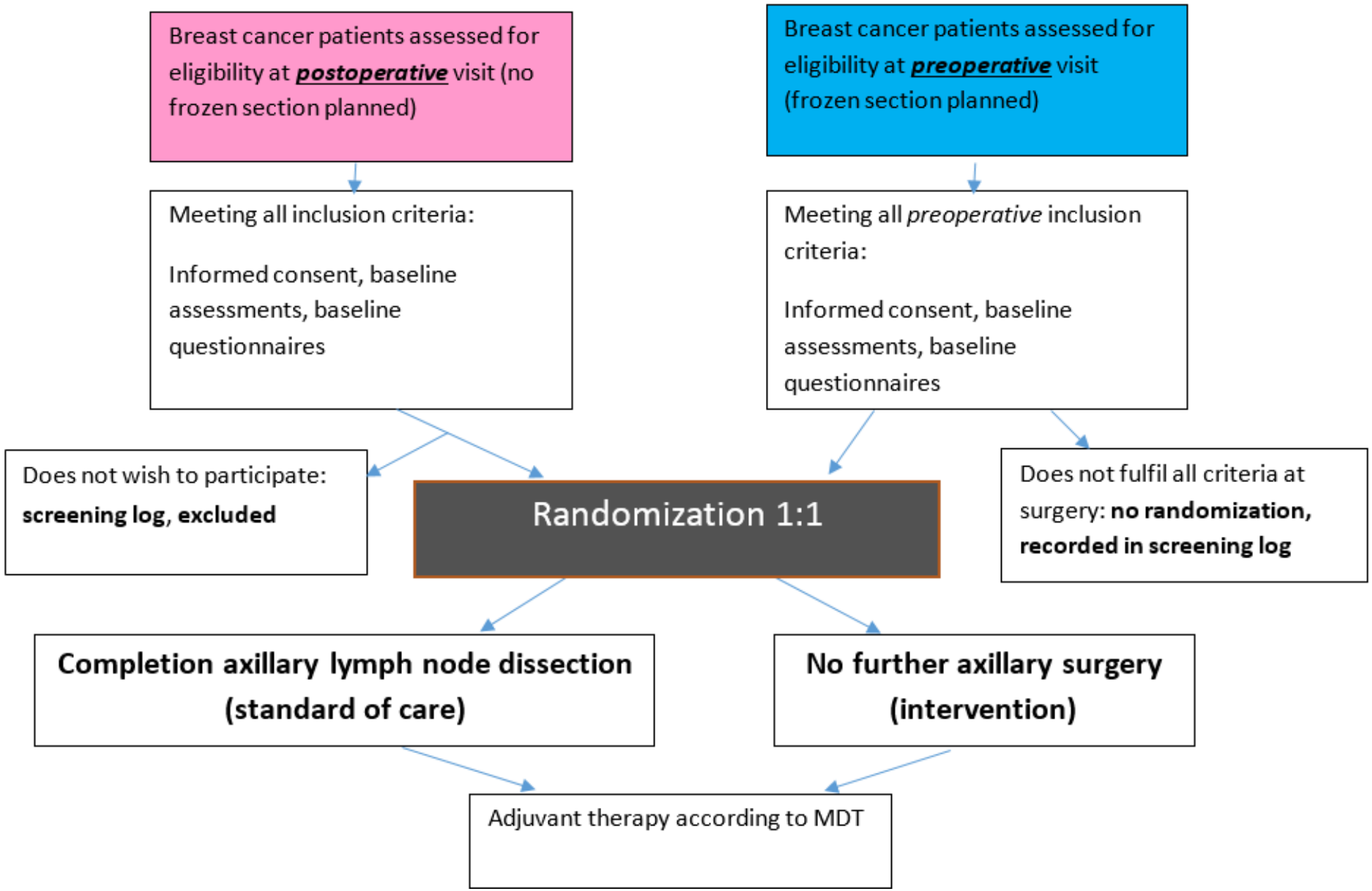
- Preoperative positive nodal cytology does not exclude participation

Exclusion criteria

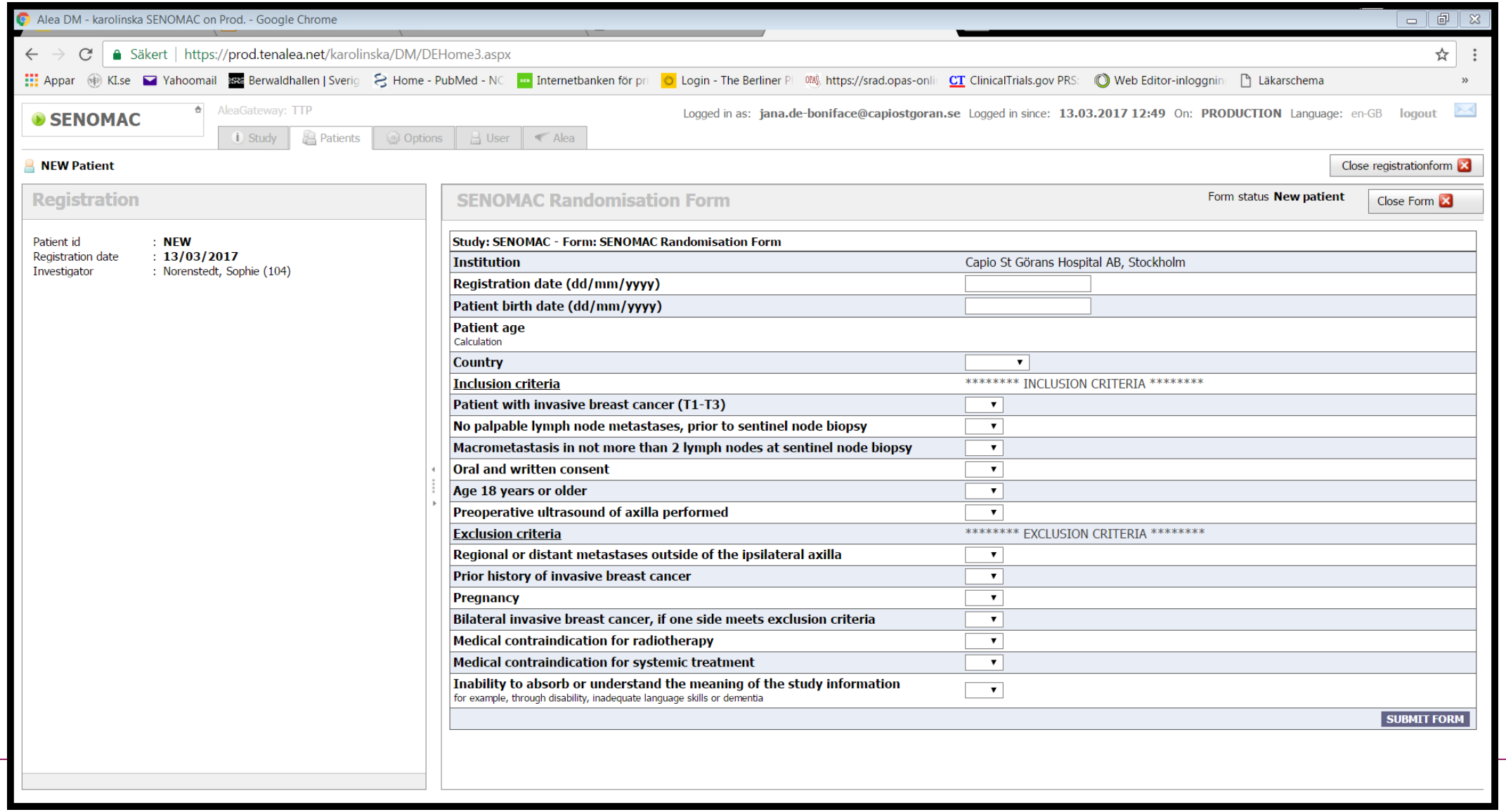
- Other regional lymph node metastases
- Distant metastases
- Previous invasive breast cancer
- Pregnancy
- Bilateral invasive breast cancer, if the other side fulfills exclusion criteria
- Medical contraindications against radiotherapy or systemic treatment

- Neoadjuvant therapy no exclusion criterion!

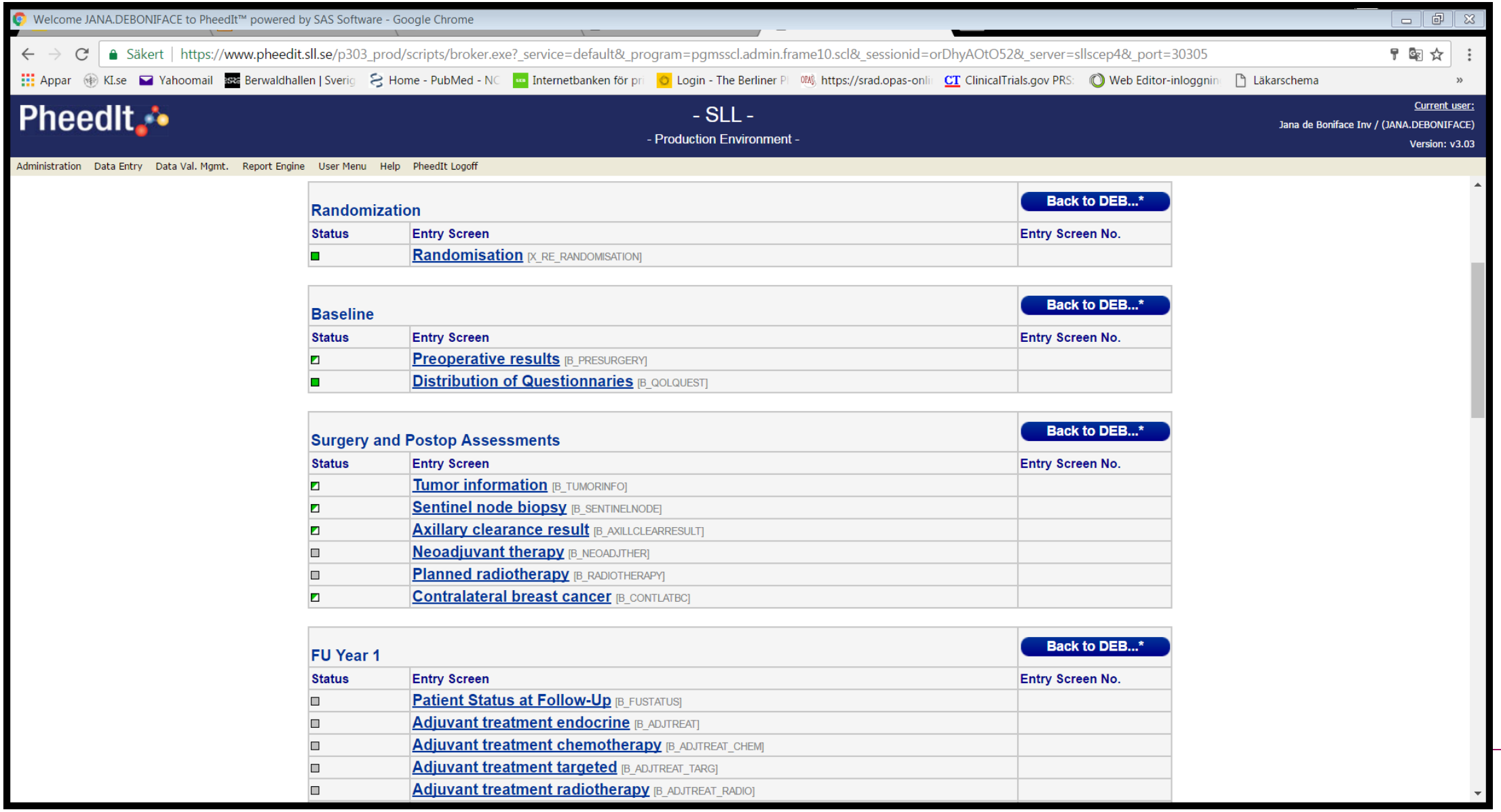
SENOMAC trial flow chart



Electronic online randomisation



Electronic case report form (eCRF) online



Adjuvant therapy

- According to national guidelines for each participating country
- Prospective registration of planned and given treatment
- **Less extensive axillary surgery must not be compensated by additional adjuvant therapy!**
- **The treatment arms are to be treated in an equivalent manner.**

Follow-up, monitoring and reimbursement

- Annual clinical examinations and mammography for 5 years, again after 10 and 15 years.
- eCRF at each follow-up visit
- Questionnaires at baseline, after 1, 3, 5 and 10 year

- Monitoring via Clinical Trials Offices (per country, data management in Stockholm) according to Good Clinical Practice

- 5000 SEK per start-up per site, 2200 SEK per correctly included and monitored patient
- Monitoring costs
- Ethical approval costs

Vetenskapsrådet

Cancerfonden

Bröstcancerföreningarnas Riksorganisation

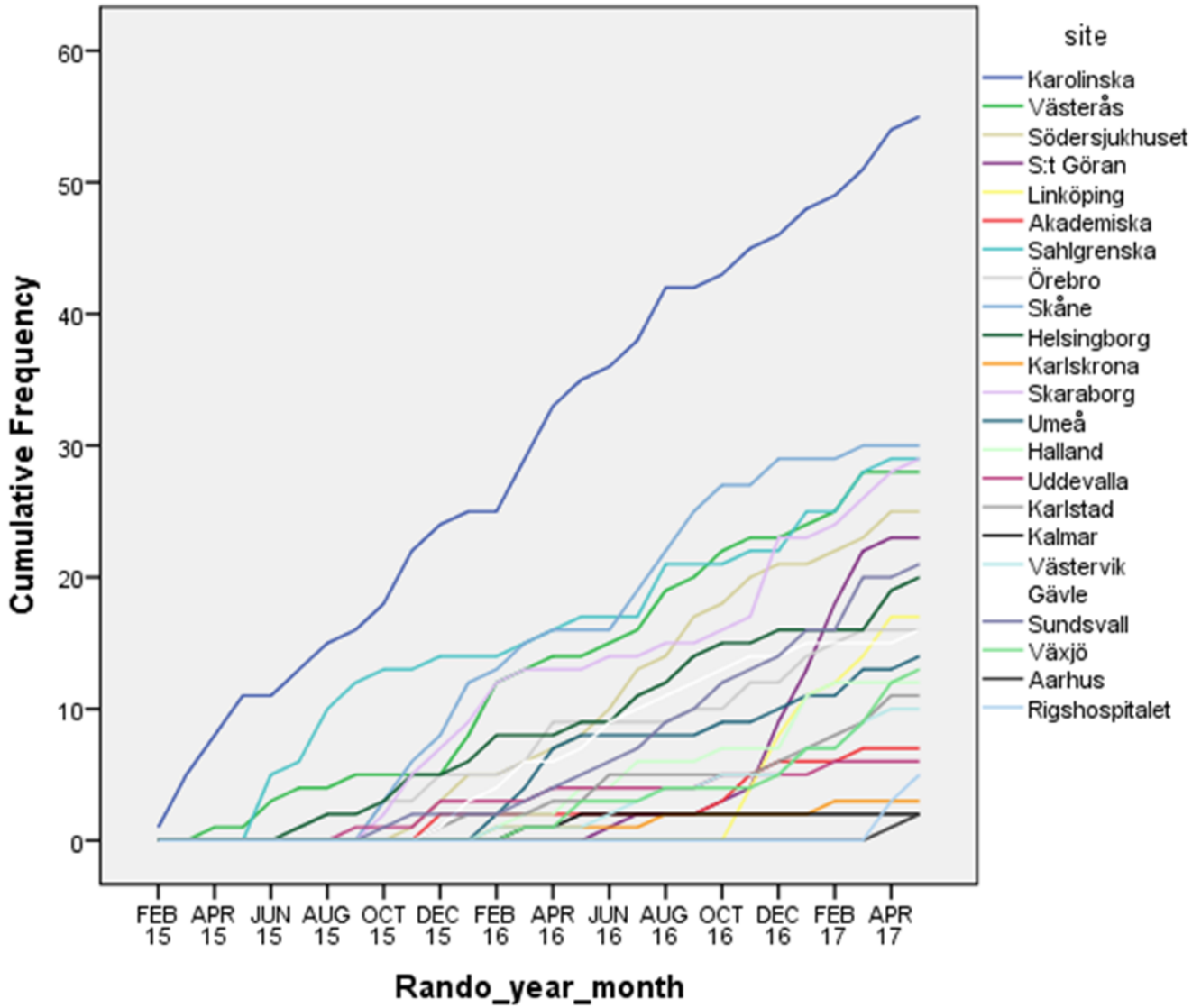
BRÖSTCANCERFONDEN

Inclusion May 2017

- 26 centers in Sweden
- 394 randomised patients

- Denmark: February 2017 (Rigshospitalet/Aarhus, 10 more sites)
- Germany: 50 centers in 2017
- Greece: 8 centers in 2017
- Austria: 20 centers in 2017
- Italy: 1 center in 2017
- Poland?
- End of inclusion 2021/22?

Current status



Queries? Comments?

THANK you for your attention