



## Neo-ACT Standard Operating Procedure

Participants

### 1. RECRUITMENT

#### *Recruitment strategies description and referral processes*

- Potential candidates can be identified at multidisciplinary team conferences. The first physician meeting the patient thereafter informs the patient about Neo-ACT. Informed consent can be obtained at the first visit or one of the following visits by either a physician or nurse, as long as it allows enough time to perform physical testing and obtain completed questionnaires prior to randomisation which must take place before the first neoadjuvant treatment.
- Information brochures and posters in the waiting rooms at the outpatient clinics. Patients can contact the Neo-ACT team via the dedicated e-mail or telephone.

#### *1.1 The physician, contact or research nurse checks for eligibility*

Use *Patient screening form Neo-ACT*.

#### *Inclusion checklist (must have all checked)*

- Patient with primary invasive breast cancer cT1-T3 cN0-2
- Full tumour biology (ER, PR, HER2) available before initiation of NACT
- Oral and written consent
- Age  $\geq 18$  years
- Ability to absorb or understand the meaning of the study

#### *Exclusion criteria (if one checked, then ineligible)*

- Bilateral invasive breast cancer
- Pregnancy or breast-feeding
- The presence of musculoskeletal, neurological, respiratory, metabolic or cardiovascular conditions that may prevent safe completion of the exercise demands of the study
- Currently performing equal to or more than 150 mins of moderate to high intensity aerobic exercise and 2 sessions per week of moderate intensity resistance exercise

Fill in the document *Subject Screening and Enrolment Log* (paper log, located on the homepage) for all individuals screened.

If participant is eligible and interested in participation, hand out the participant information and informed consent form (ICF). Note! Give two copies of the ICF so that the patient may retain one. Ask him/her to read it carefully, answer any questions, and let him/her then sign the ICF which is thereafter to be signed by physician or nurse. Please observe that in Sweden, there are different ICFs for sites in Stockholm (including biobanking) and outside Stockholm



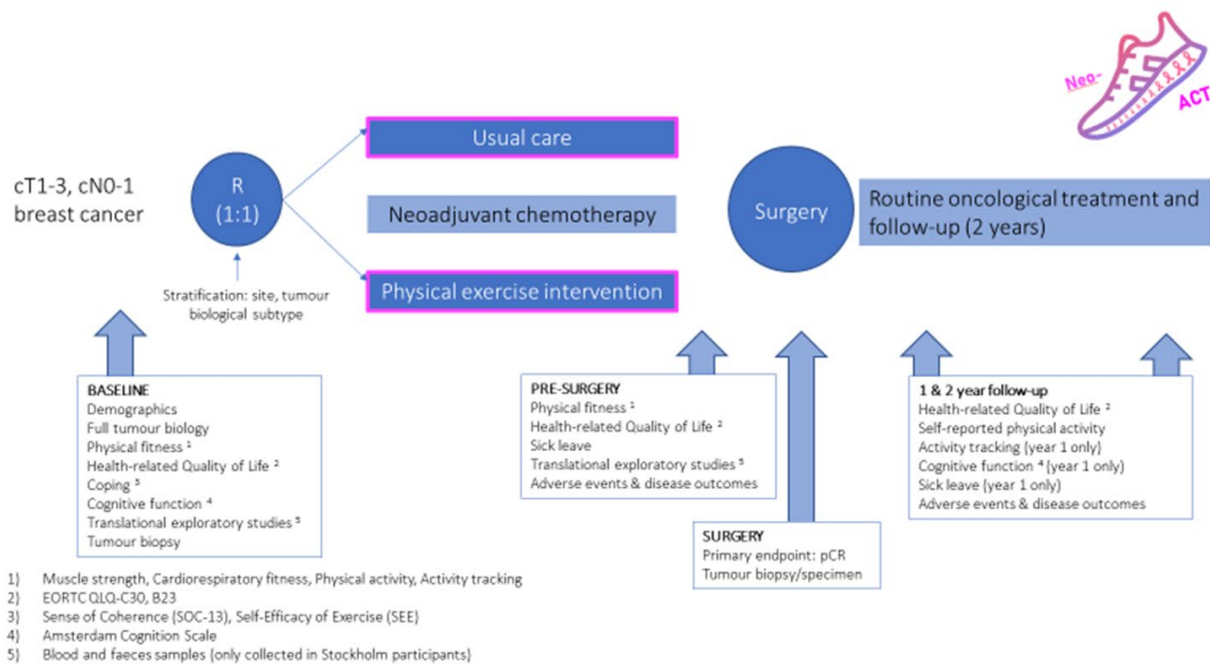
(without biobanking). For Stockholm sites, the additional consent for the use of biobanking samples for future research must be completed.

### 1.2. Booking for baseline testing

After the ICF has been signed by both participant and nurse/physician and received by the site, send/hand out the baseline questionnaire link (Dynareg) and the link for Amsterdam Cognition Scan to the participant and book participant for baseline physical testing. The date for baseline physical testing must be before the first session of NACT.

Explain that the testing session will include physical tests. Inform that they need to come in suitable clothes, be well hydrated and avoid vigorous activity and alcohol 24 hours prior. Explain that they will be randomized upon completion of the testing session.

## ASSESSMENT TIME POINTS



	Baseline	Pre-surgery	1 year	2 years
<b>Questionnaires Online</b>				
Health-related quality of life (EORTC-QLQ-C30+BR23)	X	X	X	X
Sense of Coherence (SOC-13)	X			
Self-efficacy for exercise (SEE)	X	X	X	
Self-reported physical activity (Modified Godin leisure-time exercise)	X	X	X	X
Amsterdam Cognition Scan	X		X	
<b>Physical measurements</b>				
Resting heart rate / blood pressure	X	X		
Height and weight	X	X		
Bioimpedance and body mass (optional)	X	X		
Grip strength test	X	X		
Hypothetical-12-RM Leg press test	X	X		
Exercise capacity test – Ekblom-Bak	X	X		

## 2. BASELINE QUESTIONNAIRES AND TESTING

### 2.1 Allocation of Study ID number and links to questionnaires

Allocation of the Study ID number and emailing or handing out the link to the baseline questionnaires occurs immediately after reception of the ICF signed by both participant and nurse/physician. The nurse stores the signed ICF and the participant receives two links as an email, in paper or at 1177. One link is for all questionnaires and will automatically be linked to the participant's study ID number, and one link is for the Amsterdam Cognition Scan.

To create the baseline questionnaire link for the participant:

- Log in to Dynareg <https://data.dynareg.se/neoact>
- Organisation: XXX (code for site)
- Username and password are individual (will be distributed by an administrator at Dynareg after the SIV meeting)
- Fill in the participant's Study ID number in the field **Patient ID** (XXX001, XXX002 etc) and click **OK**, then choose **Fill in new form Baseline** then click **SAVE**
- Click on **Information letter baseline** and copy the text and link to the questionnaire into an email and send to the patient. The patient is then able to, via the link, access all questionnaires



## For Amsterdam Cognition Scan

The research nurses will receive an Excel sheet including individual links for patients from the study team. The links are pre-named with patients' study IDs. The links can be copied from the excel sheet and pasted into a Word document. The link can thereafter be sent to patients by email, in paper form or via 1177.

### 2.2 Testing outline

Testing will be conducted by physiotherapists at every site.

#### *Equipment needed:*

- Testing Recording Sheet
- Pen
- Computer with internet access (for randomisation)
- Blood pressure monitor
- pulse monitor (for during exercise capacity test)
- Chair without arm rests with a straight back, placed against a wall to prevent it moving
- Grip strength dyno
- Pulse oximeter

### 2.3 Order of testing

1. **Initial check** - See how participant is feeling today, ask pre-testing questions, ask if he/she has any questions, give an overview of the session.
2. **Check contact details** - email address, phone and address. *Neo-ACT Participant Contact List* to be filled in at the completion of testing and randomisation.
3. **Check that participant has completed the online questionnaires**
  - Log in to Dynareg <https://data.dynareg.se/exmed>
  - Organisation: XXX (code for site)
  - Username and password are individual for staff
  - Fill in Patient ID (same as Study ID - XXX001, XXX002 etc) and klick OK to view if Baseline questionnaire has been completed ("Finished"). If not, remind the patient to answer the questionnaires or let them complete the questionnaires just before starting the testing.
4. **Take blood pressure and resting heart rate**
  - Feet flat, seated, not talking, taken after 5 mins of seated rest (ie after completing the questionnaires)
  - If the patient has a lymphedema no blood pressure measures should be taken from that arm



- If the patient has hypertension (systolic blood pressure >130mmHg and/or diastolic blood pressure >90mmHg), wait 1 minute and repeat the testing. Record the lower value on the testing sheet.
- Patients with severe hypertension at rest (systolic blood pressure >180mmHg and/or diastolic blood pressure >110mmHg) to be advised to contact their doctor. If severe hypertension stop testing here.

## 5. Measure height

- Remove shoes
- Patients will stand in front of the stadiometer, bare feet with heels against the wall, arms relaxed by their sides and head in horizontal plane (eyes in line with upper part of the ears)
- Assessor will slide the rod downwards until it rests on the patient's head to read height.

## 6. Bioimpedance and body mass

*Contraindications to test - having a pacemaker*

- Shoes remain off
- Instruct the patient to remove the shoes, socks and metal objects\*.  
\*Note that metal objects and electrical equipment (e.g. pacemaker) disrupt the measurement. Materials in which metal may have been incorporated need to be removed, such as jewellery, watches and / or keys in your pocket. Earrings, piercings and belts are permitted.
- Wipe the BIA foot plates and hand electrodes with the InBody wipes.
- Instruct the patient to step on the footplate barefoot with the heels on the rear sole electrodes
- Instruct the patient to grab the hand electrode so that the 4 fingers wrap the surface of the bottom hand electrode, and place the thumb on the oval electrode on the front electrodes
- Turn BIA system "ON". Avoid contact with the patient during testing. It may lead to interference affecting test results. Ensure the printer is turned on.
- Wait for the Resistance and Reactance to stabilize. Then record the computed values on the testing sheet
- Record the Body Fat Percent (PBF%), Fat Mass (kg), Lean Muscle Mass (SMM kg) and Phase Angle at 50 Hz on the test recording sheet.

## Weight

If the site does not have an Bioimpedance scale a normal scale can be used only for measuring weight.

## 7. Exercise capacity test

*Contraindications – oxygen saturation <95%, unstable angina/myocardial problems in the previous month, systolic blood pressure of more than 180 mm Hg, diastolic blood pressure of more than 100 mm Hg, resting heart rate of more than 120 bpm*

- Exercise capacity will be assessed on a cycle ergometer using the Ekblom-Bak submaximal cycle test to calculate VO<sub>2</sub>max.
- See *Ekblom-Bak testmanual elektroniskt bromsad cykel* (Testmanual\_EBtest\_sv\_elektr\_uppd20171115) for full instructions in Swedish or Finnish.
- Begin by measuring the participant's resting arterial oxygen saturation (in percent). If <95% stop testing here.
- Adjust saddle height, pedals and handlebars and explain Borg's RPE scale.
- Before starting the test, select an appropriate higher load so that the participant is assumed to reach a steady state heart rate between 120-150 beats/min (for persons < 50 years) or 110-140 beats/min (for persons ≥ 50 years) and report a general perceived physical exertion level of ≈ 14 according to Borg's RPE scale. The table below provides a guide to the choice of higher workload based on gender and activity level

	<b>Female</b>	<b>Male</b>
<b>Inactive</b>	60 W	90 W
<b>Low</b>	90 W	120 W
<b>Medium</b>	120 W	145 W
<b>High</b>	145 W	175 W

- Ask the subject to start pedalling at a cadence of 60 rpm and set resistance to 30 watts. Start the stopwatch and instruct the participant to keep cycling at 60 rpm.
- After 4 min record the participant's heart rate on the test recording sheet and increase the resistance to the previously determined higher load. Instruct the participant to keep cycling at 60 rpm.
- After 1 min of cycling at the higher load ask the participant to estimate the grade of physical exertion according to Borg's RPE scale and record on the test recording sheet (the aim is to be between 12-16).
  - If the participant indicates:*
  - < 10, increase the load by **two watt** levels and repeat the above.*
  - 10 - 11, increase load **one watt** level and repeat the above.*
  - 12 - 16, maintain the selected load and proceed to the next point.*
  - 17 or higher, stop the test and allow the participant to rest for 20 minutes before repeating the test.*
- After 4 min cycling at the higher load measure the participant's heart rate and ask them to estimate their grade of physical exertion according to Borg's RPE scale for the last 4 minutes.
- Record HR, RPE and higher load resistance on the test recording sheet.

## 8. Grip strength test

*Contraindications- fresh hand injury, painful hand/foot syndrome*

- Explain “For the test, I will ask you to squeeze this hand grip as hard as you can. You will sit or stand with a straight back and your toes pointing forward. You will hold your hand so that it’s not touching your body and squeeze the handle. I want you to try not to lean back when you squeeze. You will take a breath in, then blow out while you squeeze. You will squeeze as hard as you can until you can’t squeeze any harder.” Do a squeeze demonstration. “We will test each hand 3 times”.
- Emphasize that the patient should sit with the feet hip width apart with their toes pointing forward.
- Ask the participant, if she/he is left-handed or right-handed and record it on the testing sheet. If the participant was forced to be right-handed during childhood and is only writing with the right hand but still working with the left arm make a note on the testing sheet.
- Instruct the participant to grasp the dynamometer between the fingers, the palm at the base of the thumb and an approx. angle of 70° between forearm and upper arm. The wrist should be at 0° of ulnar/radial deviation.
- Instruct the participant to hold the dynamometer in line with the forearm at the thigh level so that it’s not touching the body.
- Instruct the participant not to hold his or her breath by explaining “Take a breath in before starting the squeeze, then slightly blow out the air during the squeeze”.
- Emphasize the quickness and hardness of the squeezing motion (with fist slightly shaking).
- Adjust handle position 2 by opening the clip, swinging the handle over and putting it in the second position. Then you swing it back and fix it again
- If handle position 2 is very uncomfortable for the participant, change the handle to a position comfortable for the participant. Record the handle position on the testing sheet. Ensure to use the same handle position for follow-up assessments.
- Explain “Now try it once just to get the feel of it. Take a breath in, let it out and squeeze.”
- Start the testing now. Explain “You may squeeze either hand first, whichever is more comfortable for you. You will do it 3 times in a row with 30 seconds rest between the trials, before conducting the test with the other hand”.
- After each trial, record the reached outcome in kg on the testing sheet and turn the dial back down to reset it. After conducting the 3 trials for each hand, select the best attempt ( $kg_{max}$ ) for the left and right hand, respectively, and record it on the testing sheet.



## 9. Hypothetical-12-RM Leg press test

*Contraindications- musculoskeletal injuries that may be exacerbated, osteoporosis, skeletal metastases in the spine or lower body*

- Adjust seat position so that knees are as close to 90° as possible.
- Feet are positioned on plate hip-wide apart with toes at the top of the plate.
- Instruct the patient to hold hand grips.





- Instruct patient to push the platform away from body by straightening legs (without completely straightening knees) and bring back to 90° position in a controlled manner.
- Instruct patient to exhale when anticipating effort, avoiding breath holding on exertion.
- Ensure full control of machine during both phases.
- Begin a warm-up consisting of 6 repetitions at low intensities with 2 minutes rest afterwards
- To determine the patient's hypothetical maximum strength, a load is chosen which can be lifted clearly a maximum of 12 times (12RM test trials). With that approach, the maximum weight and number of repetitions will be used to estimate the h1RM (according to Landers (1985)).
- Maximum of 4 trials to determine 12RM. To avoid unnecessary fatigue, aim to determine 12RM in 3 trials. All attempts should be recorded on the testing sheet.
- Rest period of 1 minute between each trial. Keep the patient motivated during the task through constant encouraging
- Extrapolating the estimated h1RM will be done using the table provided from Landers 1985. Using the excel sheet *1RM\_max\_calculator*, enter the highest weight that was successfully performed for 12 repetitions (only enter the highest weight from a completed 12 repetition set, no less). The value is automatically calculated in the column "1 RM".

### 3. RANDOMISATION AND DOCUMENTATION

#### 3.1 Randomisation

On completion of the testing session, randomise the participant directly using **ALEA Data Management (link on homepage)**. Inform the participant of randomisation result and provide appropriate information according to group allocation (see below).

Randomisation will occur on a 1:1 basis.

#### **If randomised to the intervention group:**

- Provide them with, and go through, the exercise intervention information pack including:
  - *Vitala App*
  - *Fitbit*
- Explain the procedure of how to use the Vitala App. Also, about the intensity of training (Borg's).
- Prescribe exercise in the care portal of Vitala
- Explain to the participant that she/he should contact the study team if there is any problems regarding the app or the Fitbit watch ([neoact@mmk.ki.se](mailto:neoact@mmk.ki.se)).
- Explain that we will invite them back for testing after NACT and before surgery. Prior to this visit they will receive a link to complete some of the previous questionnaires online.

#### **If randomised to the control group:**

- Provide them with a Fitbit.





- Explain that we will invite them back for testing after NACT and before surgery. Prior to this visit they will receive a link to repeat most of the previous questionnaires online.
- Inform that they will get the app for free upon completion of the trial (2 years after surgery).

## 4. INTERVENTION

### 4.1 Exercise program

The exercise group will complete 120 min home-based exercise sessions per week from initiation of NACT to surgery (approx. five months). The sessions should be at least 20 min per session. The program includes resistance and high-intensity interval training (HIIT). Patients exercise via the individualized exercise mobile application Vitala. Altogether, patients are encouraged to accumulate an additional 150 min of moderate physical activity each week, exclusive of the intervention exercise sessions.

- Participants can choose from a wide range of cardiorespiratory exercises suggested through Vitala e.g. high-intensity Tabata type activities, or stairclimbing.
- Participants are also asked to complete progressive resistance exercise from week 1 which includes ~7 exercises that target predominantly large muscle groups, e.g. chest, back, legs, biceps, triceps and abdominal muscles.
- Participants can choose which variation of the exercise to suit their preferences and to reach the intended intensity (16-18 on the Borg's scale)
- The local physiotherapist or exercise specialist has access to the mobile app's interface and contacts the participant specifically in case no activity has been logged for one week (Please see document Manual Vitala).
- The physiotherapist will support the participants to increase the intensity of their exercise gradually during the duration of the intervention with an aim to reach 16-18 on the Borg's scale.
- Weekly web-based support sessions offered by the coordinating trial committee are open to local physiotherapists or exercise specialists.

## 5. Pre-surgery

### 5.1 Questionnaires + Testing

- Questionnaire link is emailed by the site 1 week before testing and is to be completed prior to testing. Log in to **Dynareg questionnaire database**, select the participant by filling in the **Patient ID** and select correct questionnaire (**information letter** link, open the link and copy the text into the email, on paper form or in 1177 to be sent. Date for emailing out the link is in the same document as above.
- The pre-surgery visit involves the same physical tests as baseline. Check that the electronic questionnaires have been completed prior to testing. If not, make sure to remind the patient to answer the questionnaire before the tests or let them complete the questionnaires just before starting the testing.



## **6. 1-year follow-up**

### **6.1 Questionnaires**

- Questionnaire link must be emailed, sent in paper form or in 1177 to all the participants.

### **6.2 Change the password for Fitbit**

At the one-year follow-up the participants can change their password for the Fitbit. The study team will no longer download or access data from the Fitbits.

## **7. 2-year follow-up**

- Questionnaire link must be sent out by email, sent in paper form or in 1177.