



# Behavioral and Psychosocial Intervention Trials in Oncology

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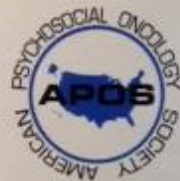


# Psycho-Oncology

THIRD EDITION

EDITED BY

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# Psychosocial interventions





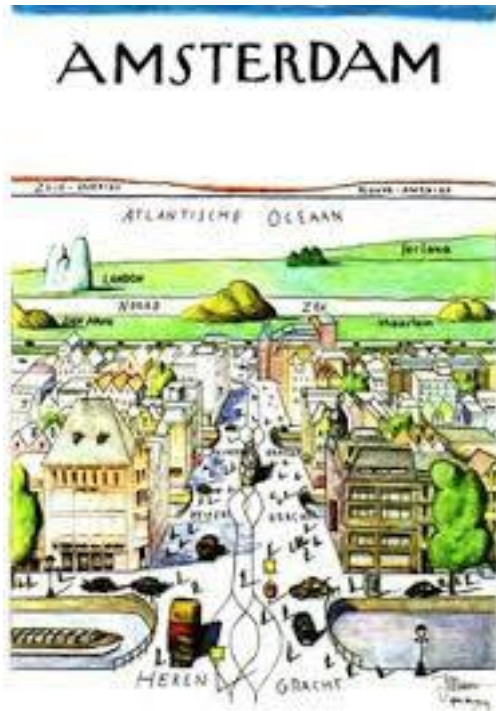
That's a tall



ORDER



# Going parochial



# Antoni van Leeuwenhoek Hospital

## The Netherlands Cancer Institute



## Efficacy of Cognitive Behavioral Therapy and Physical Exercise in Alleviating Treatment-Induced Menopausal Symptoms in Patients With Breast Cancer: Results of a Randomized, Controlled, Multicenter Trial

*Saskia F.A. Duijts, Marc van Beurden, Hester S.A. Oldenburg, Myra S. Hunter, Jacobien M. Kieffer, Martijn M. Stuiver, Miranda A. Gerritsma, Marian B.E. Menke-Pluymers, Peter W. Plaisier, Herman Rijna, Alexander M.F. Lopes Cardozo, Gertjan Timmers, Suzan van der Meij, Henk van der Veen, Nina Bijker, Louise M. de Widt-Levert, Maud M. Geenen, Gijsbert Heuff, Eric J. van Dulken, Epie Boven, and Neil K. Aaronson*



# Breast cancer and premature menopause

- 14,500 new cases annually in the Netherlands; 30% premenopausal
- Ovarian damage due to treatment; early onset of menopause
- Primary menopausal symptoms: hot flushes, night sweats, vaginal dryness, urinary incontinence
- Hot flushes prevalence rates of 63% to 80%

# Breast cancer and premature menopause

- Secondary symptoms include insomnia, weight gain, mood swings and compromised HRQL
- Menopausal symptoms related to non-compliance with maintenance anti-cancer therapy

# Medical treatments

- Hormone replacement therapy (HRT)
  - Contraindicated for patients with BC
- Non-hormonal treatment,
  - Clonidine (anti-hypertensive agent)  
30-50% decrease of hot flashes/night sweat
  - SSRI (anti-depressant agent) can be effective, but adverse effects may limit use



# Behavioral interventions

## Cognitive behavioral therapy (CBT)

- Information about symptoms
- Monitoring symptoms
- Stress management and relaxation
- Cognitive restructuring of automatic thoughts
- Encouraging helpful behavioral strategies

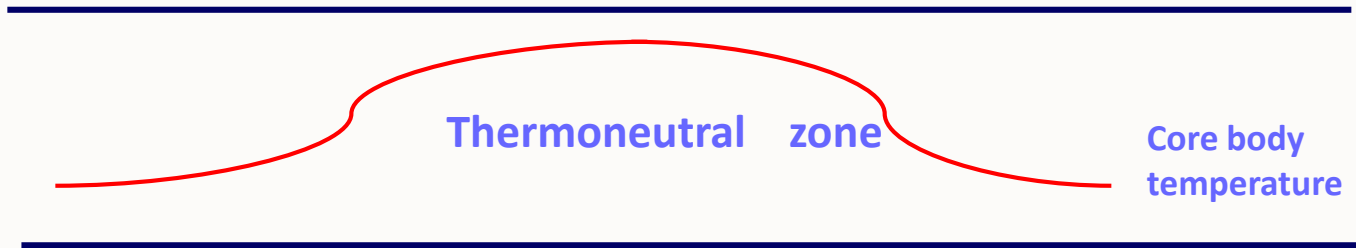
- Physical exercise (PE)

- Moderately intensive cardiovascular exercise (60-80% maximum heart rate)
- Affects thermoregulatory system

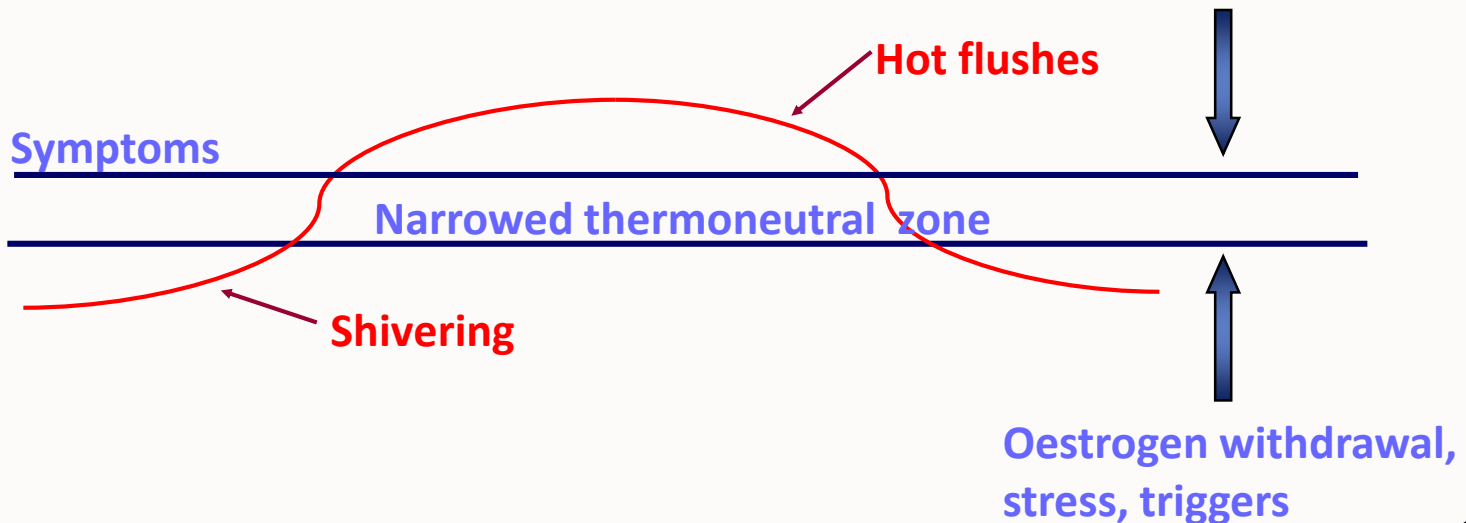
# What happens during a hot flush?

## Hot flush thresholds with and without symptoms

No symptoms



Symptoms





# Study objectives

- To evaluate, in the context of an RCT, the efficacy of CBT, PE, combination CBT/PE versus 'usual care' in reducing *menopausal symptoms* in women with primary breast cancer who undergo premature, treatment-induced menopause.
- Secondary outcomes include sexual functioning, urinary symptoms, body- and self image, psychological distress and HRQL.

# Study sample

## **Inclusion criteria:**

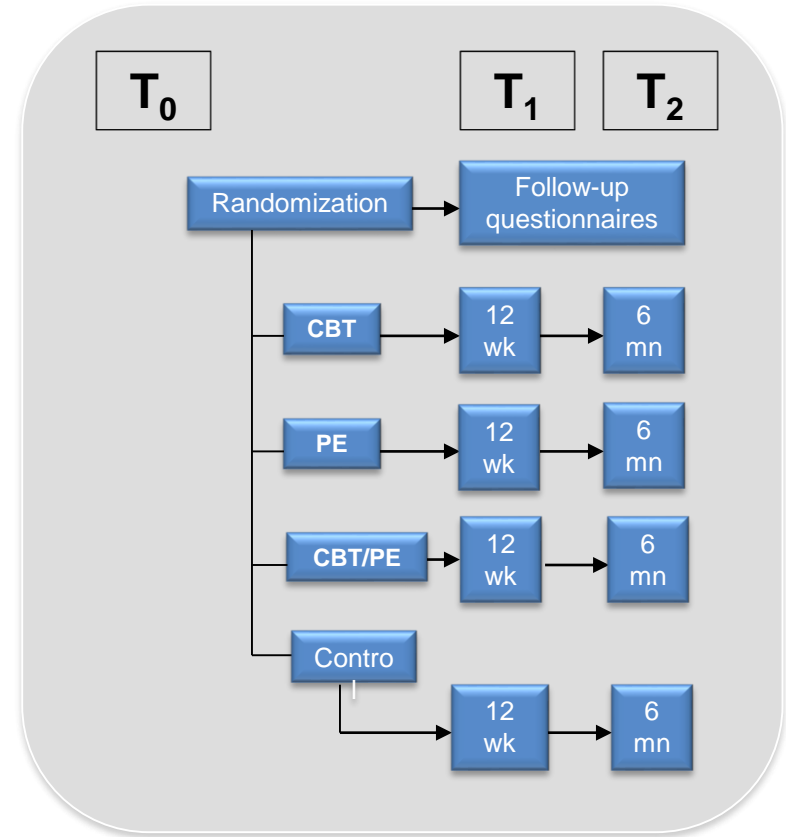
- < 50 years of age; primary breast cancer
- Premenopausal at time of diagnosis
- Completed adjuvant chemotherapy 4 months to 5 years earlier
- On-going hormonal therapy was permissible
- Disease-free at time of study entry
- Presence of hot flushes, night sweats, and/or vaginal dryness

## **Exclusion criteria:**

- Lack basic proficiency in Dutch
- Serious cognitive/ psychiatric problems and/or physical comorbidity
- BMI  $\geq$  30
- Concurrent studies directed at menopausal symptoms

# Study design and procedures

- Multicenter study (15 hospitals)
- Women identified via hospital registries
- Initial recruitment and screening by mail
- 2nd level screening by telephone
- Informed consent, baseline assessment and randomization
- Follow-up assessments



# Cognitive behavioral therapy

- 6 weekly group sessions
- 1.5 hour per session
- 6-8 participants per group
- Homework assignments (15 minutes per day)
- Social workers/ psychologists



Primary focus CBT on hot flushes, night sweats and relaxation

# Physical exercise

4 individual contacts with physiotherapist

- Intake
- Telephone contact (2x)
- Evaluation
- Individually tailored
- 2.5-3 hours per week; 12 weeks
- 60-80% maximum heart rate
- Heart rate monitor





# Outcome measures

## Primary Outcomes

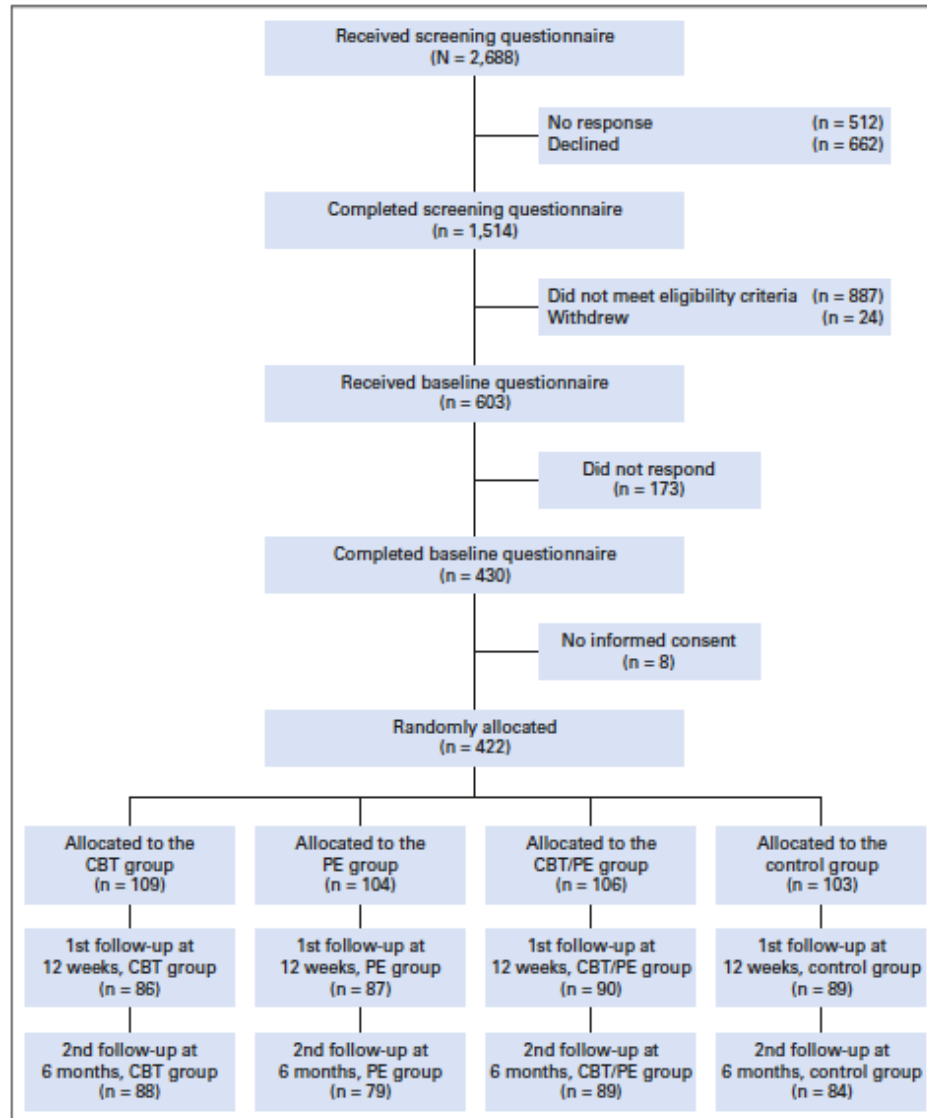
- Menopausal symptoms (FACT-ES)
- Vasomotor symptoms (Hot Flush Rating Scale)
  - HF/NS frequency
  - HF/NS bother

## Secondary Outcomes

- Urinary symptoms (BFLUTS)
- Sexuality (SAQ)
- Body image & self-image (QLQ-BR23)
- Psychological distress (HADS)
- Generic health-related quality of life (SF-36)

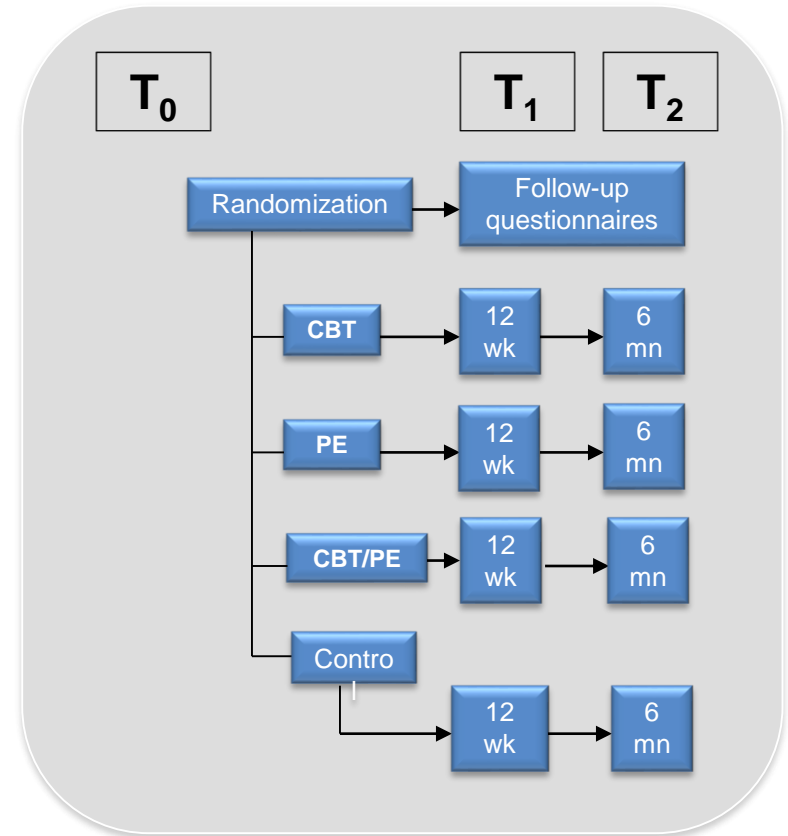


# Consort diagram of patient recruitment



# Patient recruitment

- 2688 women approached
- 1514 (56%) responded
- 603 met eligibility criteria (motivated and symptomatic)
- N = 422

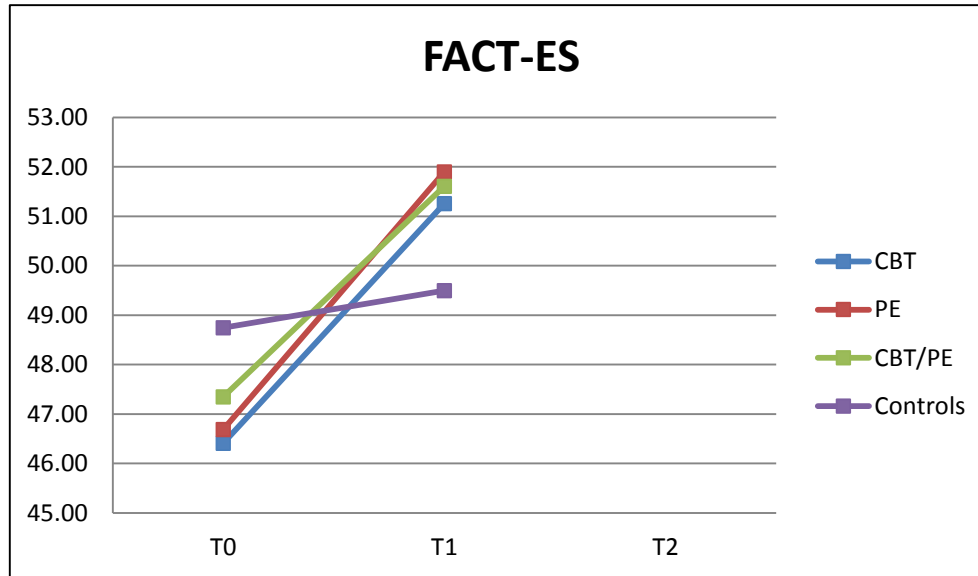


# Patient sociodemographic and clinical characteristics

Sociodemographic/ Life style	Total Sample (N = 422)
Age mean (SD)	48.2 (5.7)
Married	81%
College educated	38%
Working	75%
BMI mean (SD)	25 (4)
Smoker	17%
Exercise/wk (%)	
- Never	20
- 1-3 times	60
- $\geq 4$ times	20

Clinical	Total Sample (N = 422)
Mastectomy	50%
Chemotherapy	91%
> 1 yr since completion of chemo	81%
Hormonal therapy	86%
Sleep medication or anti- depressants	22%
Hot flashes/ day <sub>mean (SD)</sub>	25 (4)

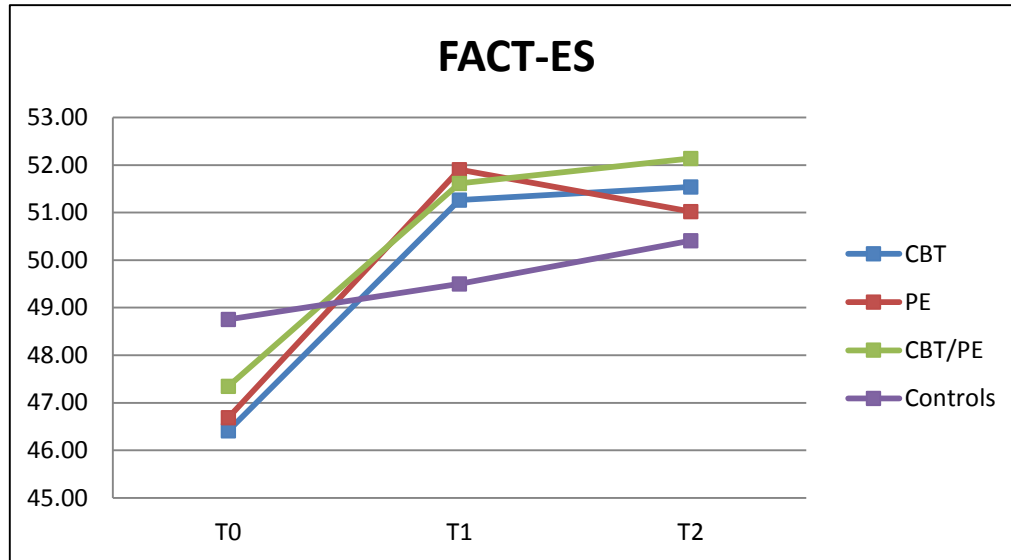
# Endocrine symptoms



	Mean diff T1	SE	ES
CBT vs UC	4.1	.95	0.48
PE vs UC	4.5	.96	0.52
CBT/PE vs. UC	3.5	.95	0.41



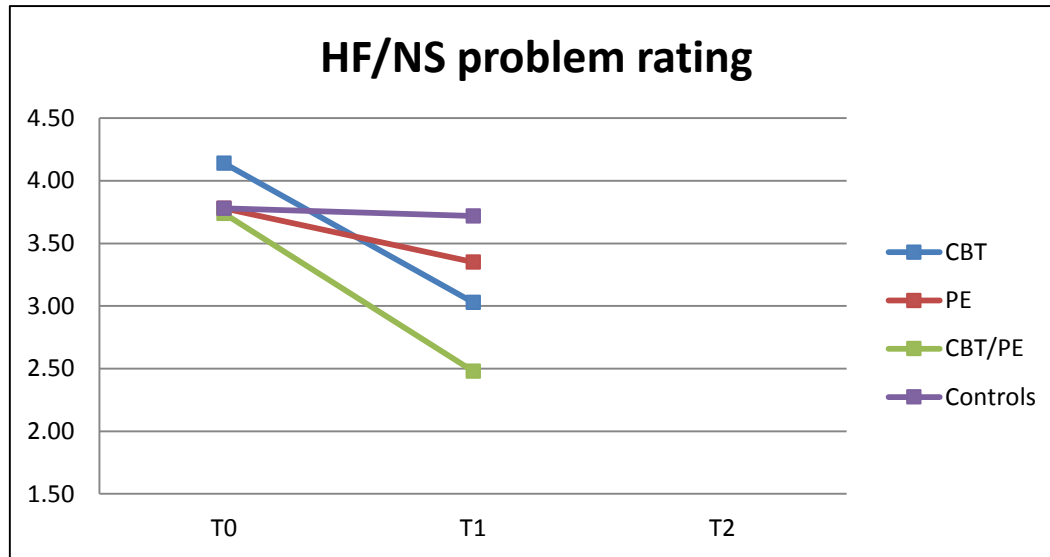
# Endocrine symptoms



	Mean diff T1	SE	ES
CBT vs UC	-4.1	.95	0.48
PE vs UC	-4.5	.96	0.52
CBT/PE vs. UC	3.5	.95	0.41

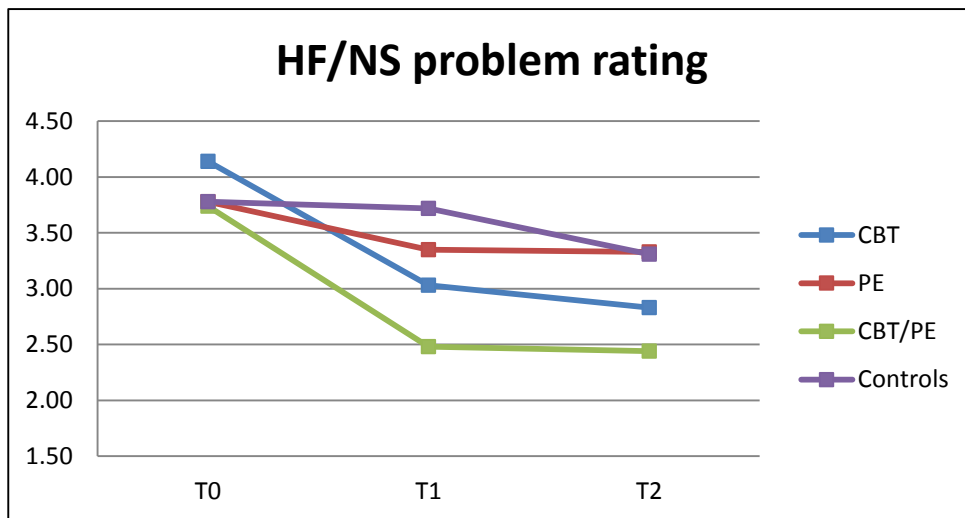
	Mean diff T2	SE	ES
CBT vs UC	3.5	.96	0.40
PE vs UC	2.7	.98	0.31
CBT/PE vs. UC	3.1	.96	0.36

# Hot flushes/night sweats



	Mean diff T1	SE	ES
CBT vs UC	-1.1	.24	0.49
PE vs UC	-0.4	.24	0.17
CBT/PE vs. UC	-1.2	.24	0.56

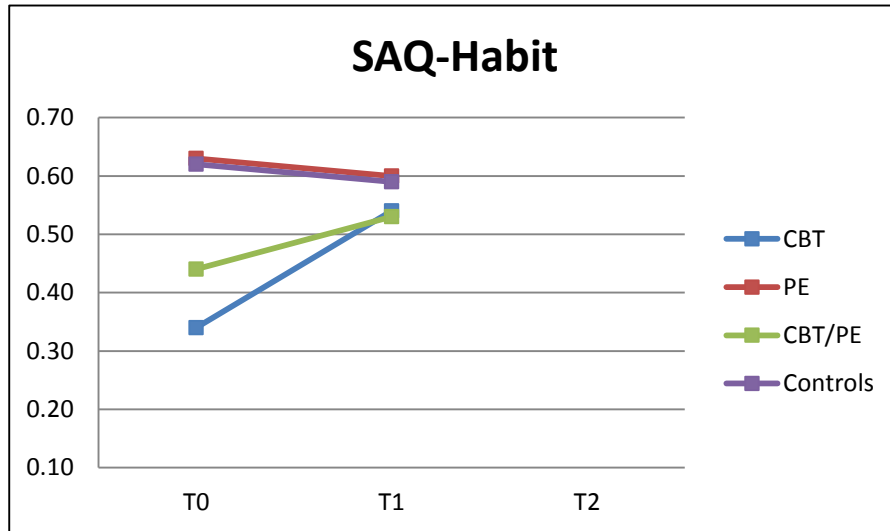
# Hot flushes/night sweats



	Mean diff T1	SE	ES
CBT vs UC	-1.1	.24	0.49
PE vs UC	-0.4	.24	0.17
CBT/PE vs. UC	-1.2	.24	0.56

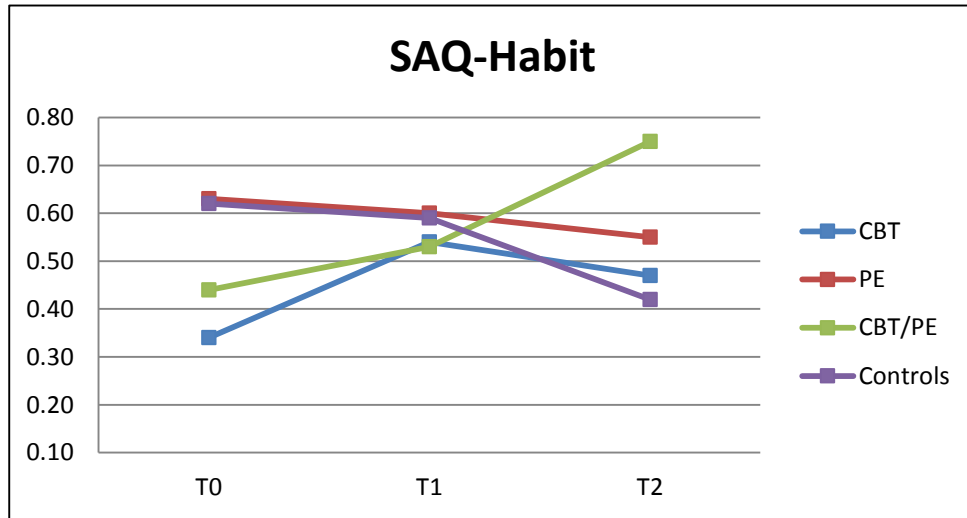
	Mean diff T2	SE	ES
CBT vs UC	-0.9	.24	0.40
PE vs UC	-0.1	.25	0.01
CBT/PE vs. UC	-0.8	.24	0.39

# Sexual activity



	Mean diff T1	SE	ES
CBT vs UC	0.2	0.2	0.31
PE vs UC	0.0	0.2	0.0
CBT/PE vs. UC	0.1	0.2	0.20

# Sexual activity



	Mean diff T1	SE	ES
CBT vs UC	0.2	0.2	0.31
PE vs UC	0.0	0.2	0.01
CBT/PE vs. UC	0.1	0.2	0.15

	Mean diff T1	SE	ES
<b>CBT vs UC</b>	0.33	0.2	0.42
PE vs UC	0.1	0.2	0.15
<b>CBT/PE vs UC</b>	0.5	0.2	0.6



# Other outcomes

- Additional significant effects were observed for:
  - urinary symptoms
  - physical functioning
- No significant effects for:
  - Body image
  - Psychological distress
  - Other HRQOL domains

# Per protocol analysis

- Yielded results similar to those based on ITT
- Additional significant effects were observed for:
  - HF/NS frequency ratings
  - Sexual pleasure
  - Role-emotional functioning
  - Mental health
  - Vitality
- Most additional effects observed in groups including CBT

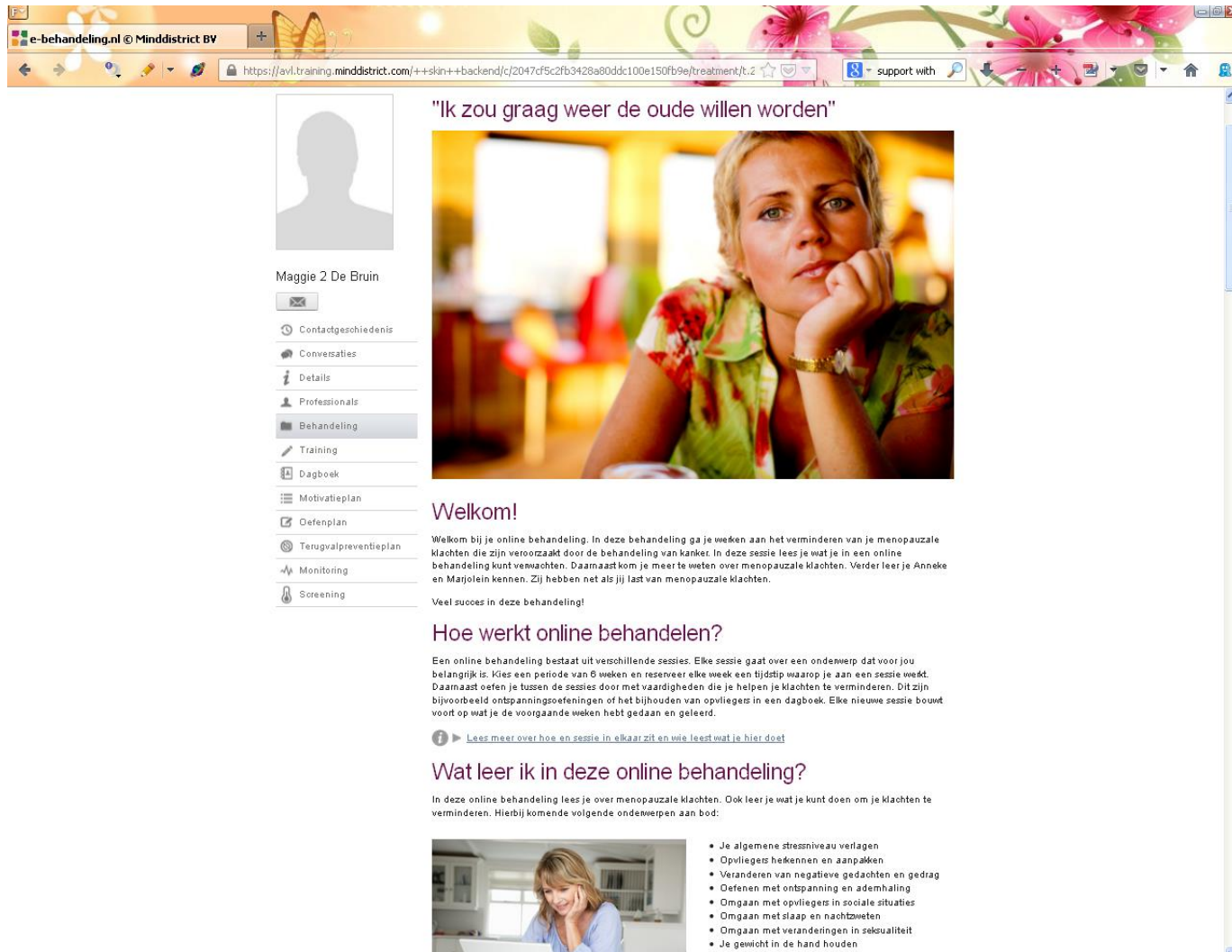
# Conclusions

- CBT and PE, either alone or in combination, have a clinically significant, salutary effect on menopausal and urinary symptoms
- Sexuality is also positively affected, particularly by CBT
- PE has a sustained, positive effect on physical functioning

# Internet-based CBT Program

- Closed environment: patients can only participate after completing a screening questionnaire
- Interactive: patients have homework assignments, can watch video clips of experts and patients, and listen to relaxation exercise instructions
- Guided vs. unguided: patients undergo a telephone intake interview with a counselor and receive feedback via email on their homework from this counselor

# Session 1



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support with

Maggie 2 De Bruin

Contactgeschiedenis

Conversaties

Details

Professionals

Behandeling

Training

Dagboek

Motivatieplan

Defenplan

Terugvalpreventieplan

Monitoring

Screening

"Ik zou graag weer de oude willen worden"

Welkom!

Welkom bij je online behandeling. In deze behandeling ga je weken aan het verminderen van je menopauzale klachten die zijn veroorzaakt door de behandeling van kanker. In deze sessie lees je wat je in een online behandeling kunt verwachten. Daarnaast kom je meer te weten over menopauzale klachten. Verder leer je Anneke en Manjolein kennen. Zij hebben net als jij last van menopauzale klachten.

Veel succes in deze behandeling!

Hoe werkt online behandelen?

Een online behandeling bestaat uit verschillende sessies. Elke sessie gaat over een onderwerp dat voor jou belangrijk is. Kies een periode van 6 weken en reserveer elke week een tijdstip waarop je aan een sessie werkt. Daarnaast oefen je tussen de sessies door met vaardigheden die je helpen je klachten te verminderen. Dit zijn bijvoorbeeld ontspanningsoefeningen of het bijhouden van opvliegers in een dagboek. Elke nieuwe sessie bouwt voort op wat je de voorgaande weken hebt gedaan en geleerd.


[▶ Lees meer over hoe een sessie in elkaar zit en wie leest wat je hier doet](#)

Wat leer ik in deze online behandeling?


In deze online behandeling lees je over menopauzale klachten. Ook leer je wat je kunt doen om je klachten te verminderen. Hierbij komende volgende onderwerpen aan bod:

- Je algemene stressniveau verlagen
- Opvliegers herkennen en aanpakken
- Veranderen van negatieve gedachten en gedrag
- Oefenen met ontspanning en ademhaling
- Omgaan met opvliegers in sociale situaties
- Omgaan met slaap en nachtzweten
- Omgaan met veranderingen in seksualiteit
- Je gewicht in de hand houden

# Session 4



Maggie 2 De Bruin



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## "Die zweetaanvallen verpesten mijn nacht"



### Wat ga je vandaag doen?

's Nachts wakker worden door nachtelijke zweetaanvallen is vervelend. In deze sessie leer je hoe je het beste om gaat met een nachtelijke zweetaanval. Daarnaast leer je wat je allemaal wel en niet moet doen om je nachtrust kunt verbeteren.

Veel succes!

### Goed slapen lijkt eenvoudig

Slapen lijkt zo eenvoudig. Je gaat liggen, doet je ogen dicht en als je je ogen weer open doet is het de volgende dag. Voor veel mensen is dit niet vanzelfsprekend. Sommige mensen hebben moeite met in slaap vallen. Anderen slapen makkelijk in, maar worden midden in de nacht wakker en kunnen dan niet meer verder slapen. Bijvoorbeeld bij een nachtelijke zweetaanval. Het is belangrijk dat je leert hier rustig mee om te gaan. Daarnaast is het belangrijk de kans op een nachtelijke zweetaanval te verminderen. Dit doe je door jezelf goede slaapgewoonten aan te leren. Deze gewoonten noem je slaaphygiëne.

### Tips en feiten over slapen

Er bestaan veel misverstanden over slapen. Lees onderstaande tips en feiten over slapen:

Feiten	Tips
<ul style="list-style-type: none"><li>De eerste 4 uur van je slaap heb je de diepe slaap. Dit is het belangrijkste gedeelte waarin je uitrust en herstelt.</li><li>De meeste mensen denken dat ze meer slaap nodig hebben dan eigenlijk het geval is. Maar na een nacht slecht slapen houd je de dag vaak beter vol dan je denkt.</li><li>Slaapproblemen zijn niet gevaarlijk.</li><li>De meeste mensen voelen zich nog steeds moe als ze wakker worden.</li><li>Het is normaal om je op sommige dagen niet helemaal uitgerust te voelen. Ook nadat je een</li></ul>	<ul style="list-style-type: none"><li>Heb je slecht geslapen? Doe gewoon de dingen die je anders ook doet. De structuur van de dag helpt je er wel doorheen.</li><li>Houd je verwachtingen realistisch; iedereen heeft af en toe wel eens een slechte nacht.</li><li>Als je langer dan 15 minuten wakker ligt, ga dan je bed uit en doe iets rustigs. Ga weer terug naar bed als je merkt dat je moe wordt.</li></ul>

# Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial

*Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Edwin Geleijn, Jacobien M. Kieffer, Laurien M. Buffart, Marianne de Maaker-Berkhof, Epie Boven, Jolanda Schrama, Maud M. Geenen, Jetske M. Meerum Terwogt, Aart van Bochove, Vera Lustig, Simone M. van den Heiligenberg, Carolien H. Smorenburg, Jeannette A.J.H. Hellendoorn-van Vreeswijk, Gabe S. Sonke, and Neil K. Aaronson*

# Exercise and cancer



- ↑ Physical functioning
  - Cardiorespiratory fitness
  - Muscle strength



- ↓ Fatigue



- ↑ Health-related quality of life



- ↑ Treatment tolerability?



# Questions still to be addressed:

- Which exercise for which patient?
  - Optimal dose (high or low intensity)
  - Type (aerobic + resistance versus aerobic only)
  - Timing (before, during or after active treatment)
  - Length of exercise prescription
- Effect on treatment tolerability
- Cost-effectiveness
  - Return to work
  - Hospital visits
  - Medication requirements

# Aim PACES

Evaluation of the (cost-)effectiveness of two exercise programs

- Onco-Move
  - low intensity
  - home-based physical activity program
- OnTrack
  - high intensity
  - supervised exercise program

in patients undergoing adjuvant chemotherapy

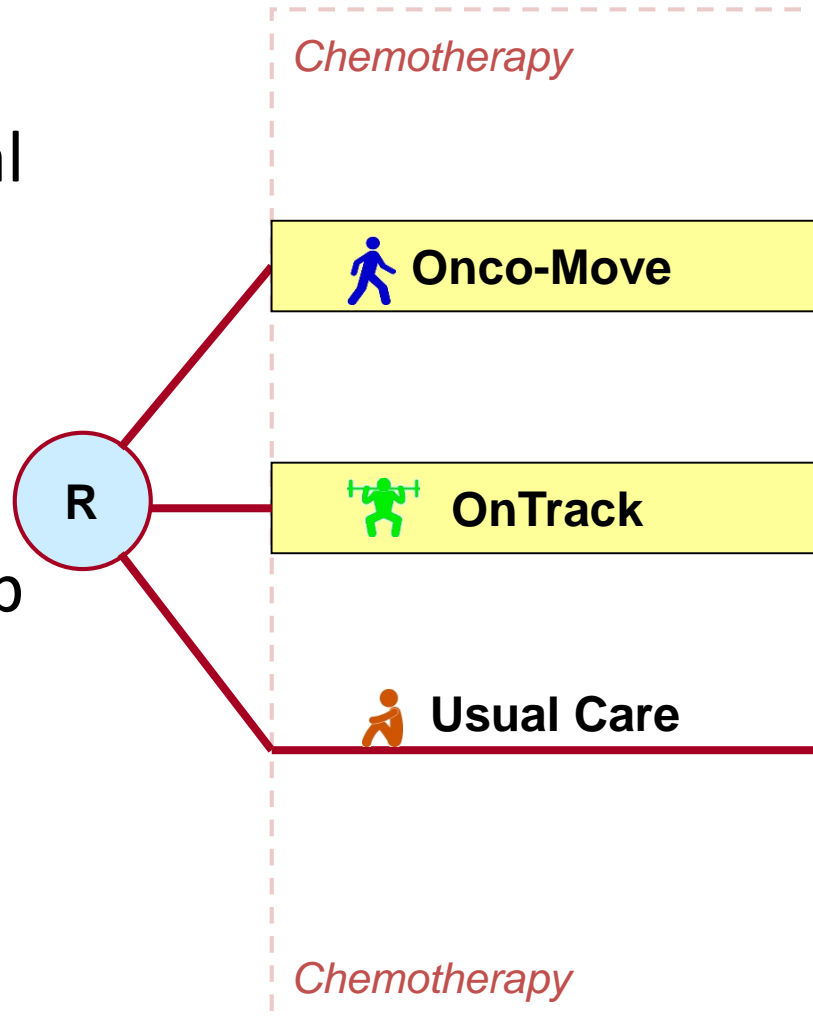
# Design

Multi-center (12)  
randomized controlled trial

- 2 intervention groups
  - Onco-Move
  - OnTrack
- Usual Care control group

Stratified by:

- Hospital
- Diagnosis
- Trastuzumab use



# Intervention: Onco-Move

*Low intensity, home-based physical activity program*

- Nurse specialist/ oncology nurses
- 30 minutes of daily activity
- *Walking, cycling, ..*



# Intervention: OnTrack



*High intensity, supervised exercise program*

- Physical therapist
- 2 sessions per week:
  - muscle strength exercises
    - 70 – 80% 1RM (20 min)
  - aerobic exercises
    - 50 – 80% Wmax (30 min)
- 30 minutes of daily activity



# Participants

- Primary breast or colon cancer
- Scheduled to undergo adjuvant chemotherapy
- Minimal age 18
- No comorbid conditions that would contraindicate participation in an exercise program
- Basic fluency in Dutch

# Primary outcome measures (1 of 2)

## Physical fitness

- Cardiorespiratory fitness
  - Steep Ramp Test ( $W_{max}$ )
  - Exercise Endurance Test (time)
- Muscle strength
  - Isometric break test
    - Knee extension (Nm)
    - Elbow flexion (Nm)



# Primary outcome measures (2 of 2)

## Fatigue

- Multidimensional Fatigue Inventory (MFI)
  - 5 domains
    - General
    - Physical
    - Reduced Activity
    - Reduced Motivation
    - Mental
- Fatigue Quality List (FQL)
  - 4 domains
    - Frustrating
    - Exhausting
    - Pleasant
    - Frightening



# Primary outcome measures (2 of 2)

## Fatigue

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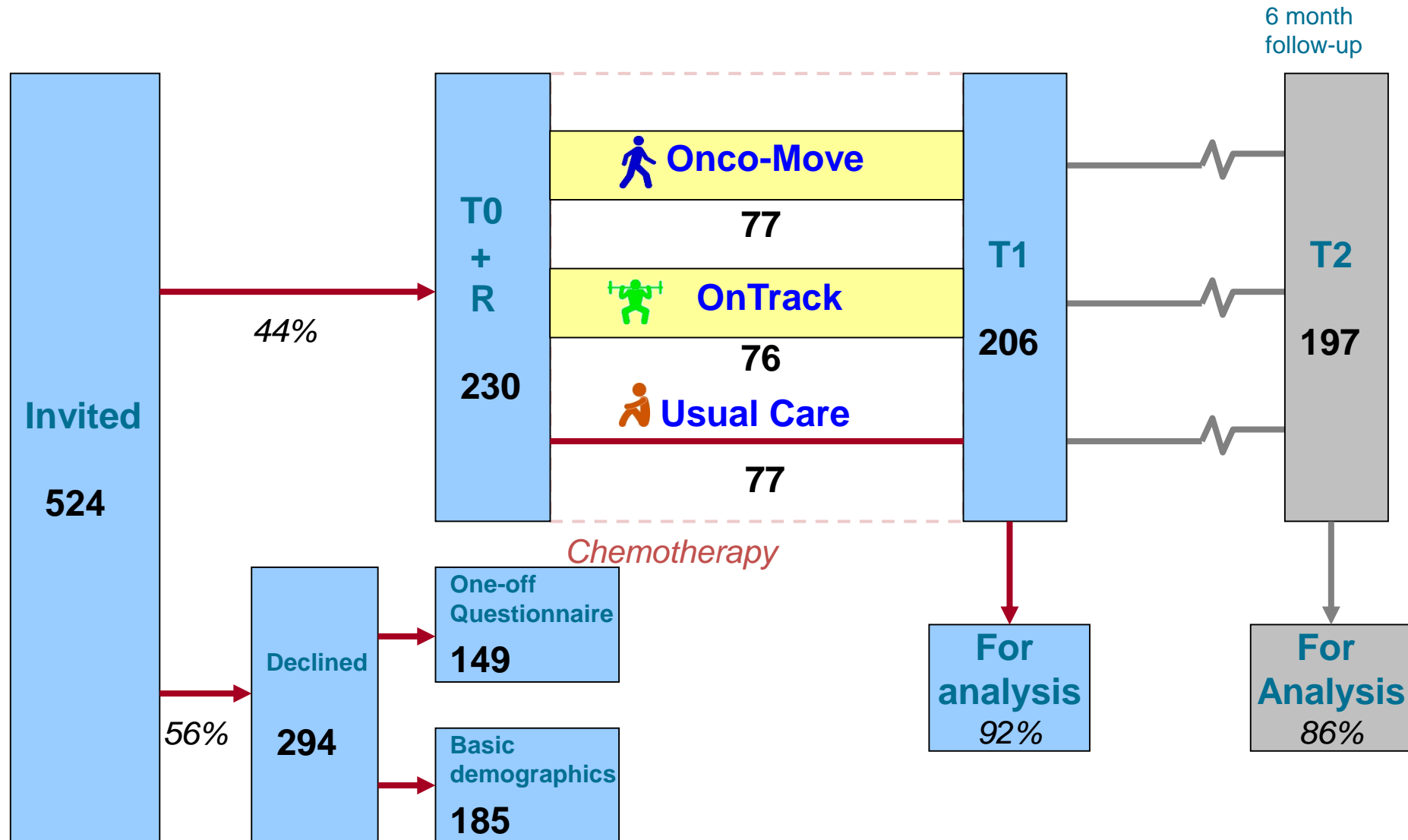
# Secondary outcome measures

- Chemotherapy completion rates
- Health-related quality of life (EORTC QLQ-C30)
- Mood disturbance (HADS)
- Quality of sleep (PSQI)
- Functioning in daily life (IPA)
- Physical activity level (PASE and accelerometer)
- Compliance
- Satisfaction
- Cost-effectiveness

# Secondary outcome measures

- Chemotherapy completion rates
- Health-related quality of life (EORTC QLQ-C30)
- Mood disturbance (HADS)
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# Breast cancer patient participation

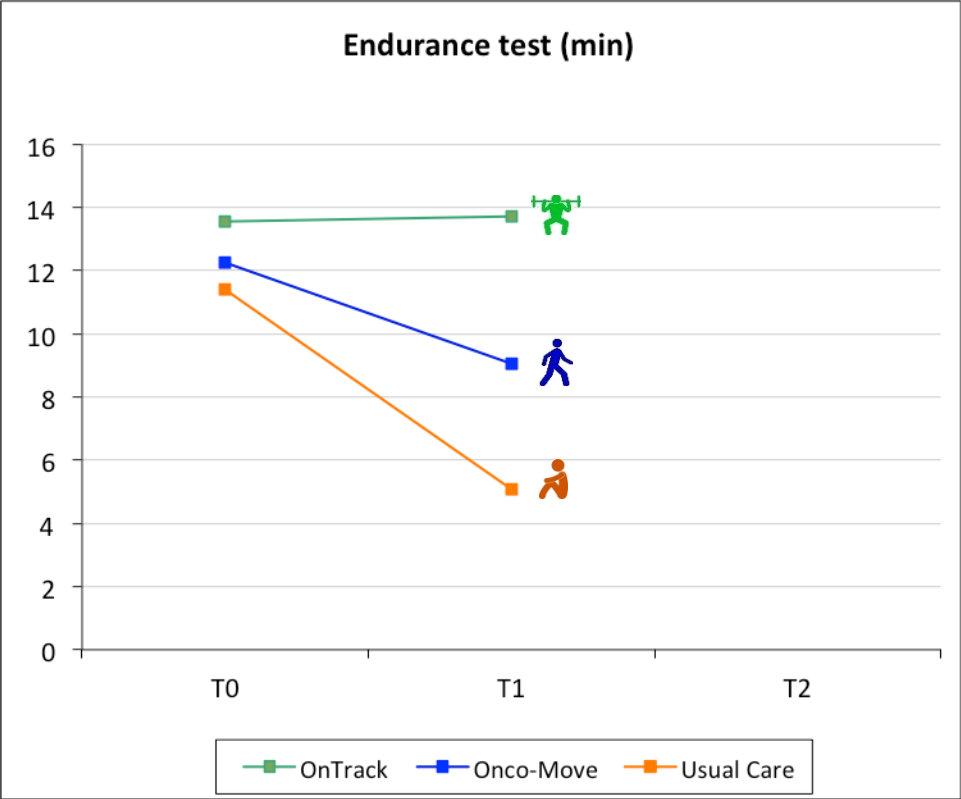






# Sample characteristics (N = 230)

Mean age (SD)	51 years (9 yrs)
Marital status	78% married
Education	55% college/university
Work	69% employed
Cancer stage	
Stage I	6%
Stage II or III	94%
Locoregional treatment	
Breast conserving surgery	77%
Axillary lymph node dissection	31%
Radiotherapy	78%

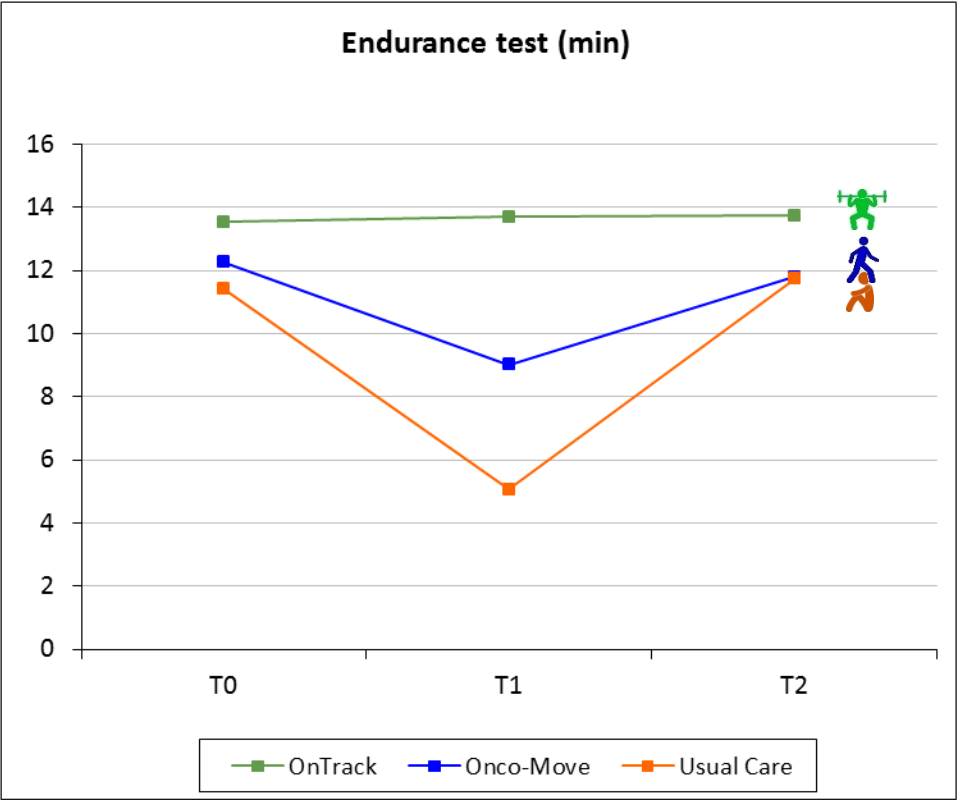
No significant group differences in background characteristics





# Cardiorespiratory fitness







	Mean diff T1	95% CI		ES
 <b>OnTrack</b>  <b>Usual Care</b>	8.0	5.7	10.2	0.90
 <b>OncoMove</b>  <b>Usual Care</b>	3.9	2.0	5.9	0.45

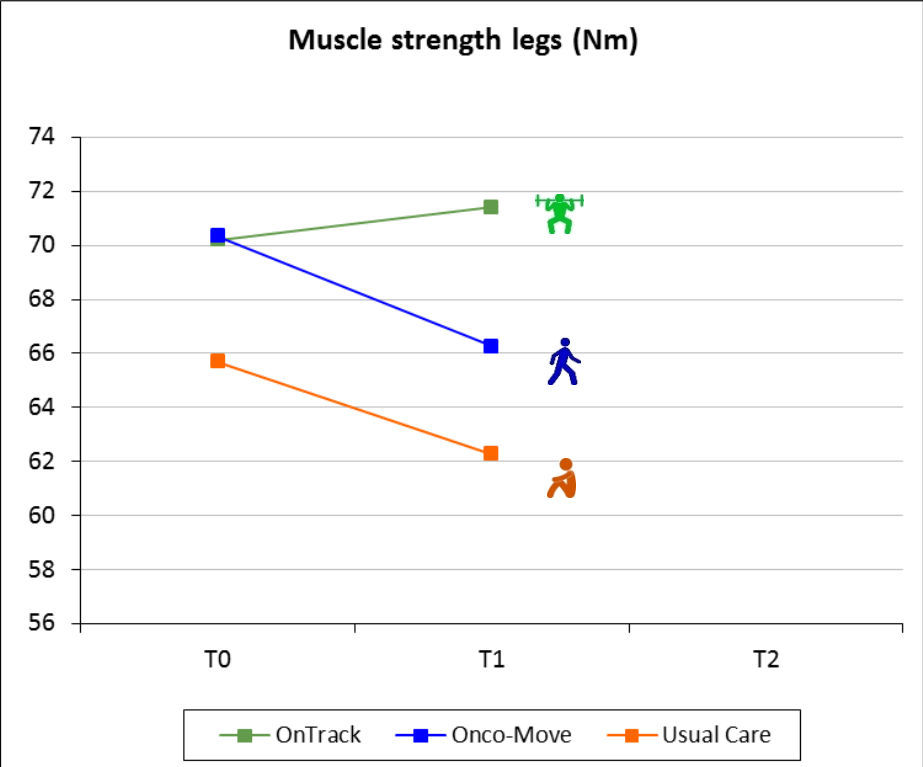
# Cardiorespiratory fitness







	Mean diff T1	95% CI		ES
<div> </div> <div>OnTrack Usual Care</div>	8.0*	5.7	10.2	0.90
<div> </div> <div>OncoMove Usual Care</div>	3.9*	2.0	5.9	0.45

	Mean diff T2	95% CI		ES
<div> </div> <div>OnTrack Usual Care</div>	1.2	-1.4	3.7	0.13
<div> </div> <div>OncoMove Usual Care</div>	-0.1	-2.6	2.3	0.01

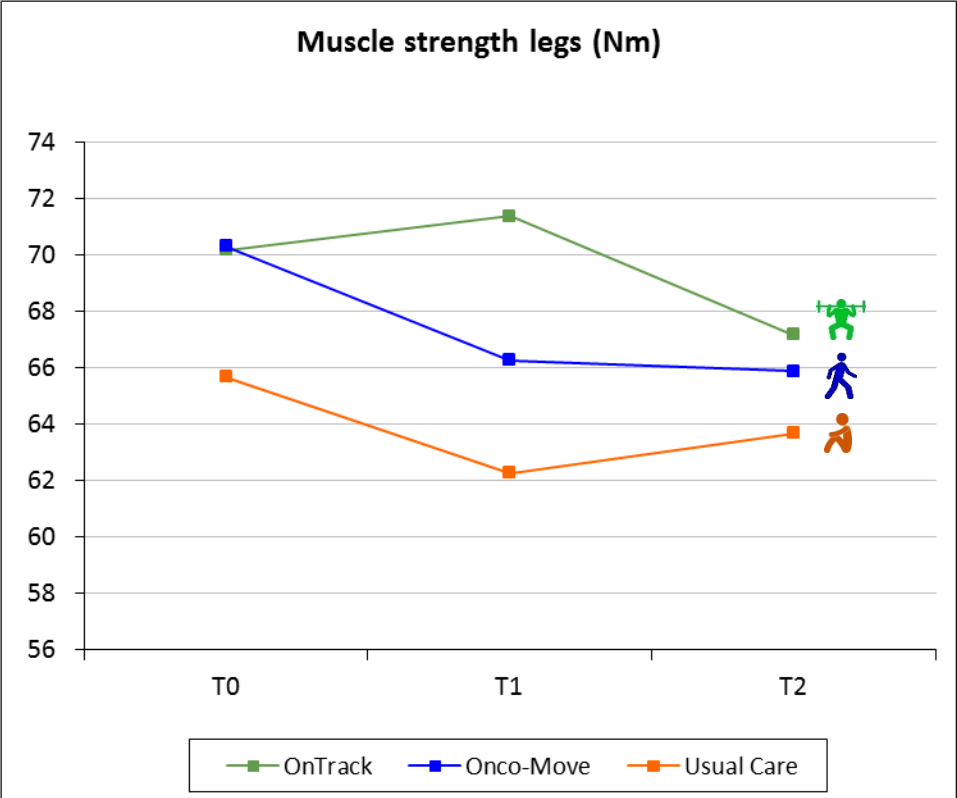
# Muscle strength











	Mean diff T1	95% CI		ES
<div> <b>OnTrack</b></div> <div> <b>Usual Care</b></div>	7.6	2.1	13.0	0.38
<div> <b>OncoMove</b></div> <div> <b>Usual Care</b></div>	2.1	-3.4	7.7	0.10



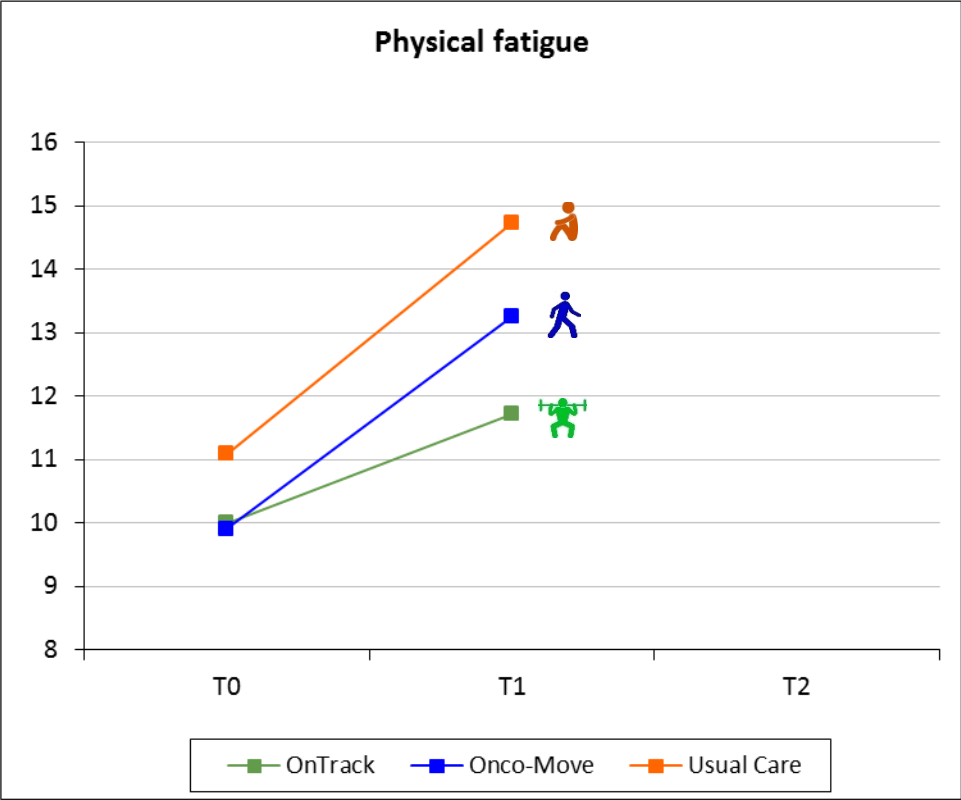
# Muscle strength




	Mean diff T1	95% CI		ES
 <b>OnTrack</b>  <b>Usual Care</b>	7.6	2.1	13.0	0.38
 <b>OncoMove</b>  <b>Usual Care</b>	2.1	-3.4	7.7	0.10

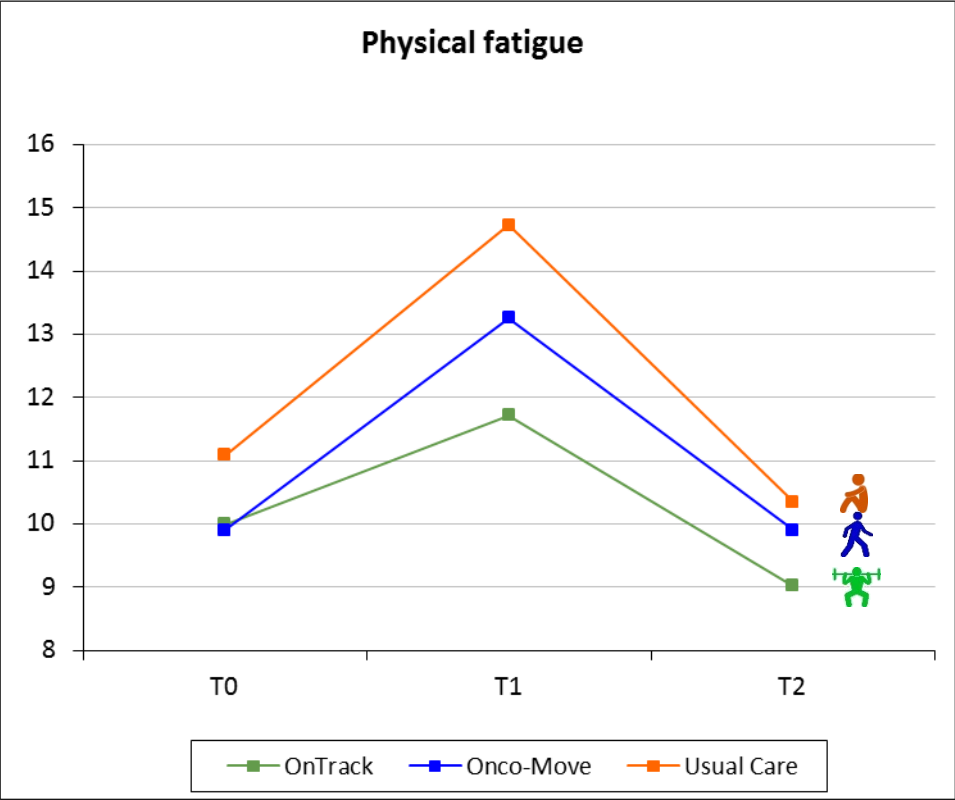
	Mean diff T2	95% CI		ES
 <b>OnTrack</b>  <b>Usual Care</b>	1.1	-4.8	7.0	0.06
 <b>OncoMove</b>  <b>Usual Care</b>	-0.4	-6.2	5.5	0.02


# Fatigue (MFI)







	Mean diff T1	95% CI		ES
 <b>OnTrack</b> <b>Usual Care</b>	-2.7	-4.0	-1.4	0.63
 <b>OncoMove</b> <b>Usual Care</b>	-1.1	-2.4	0.2	0.28

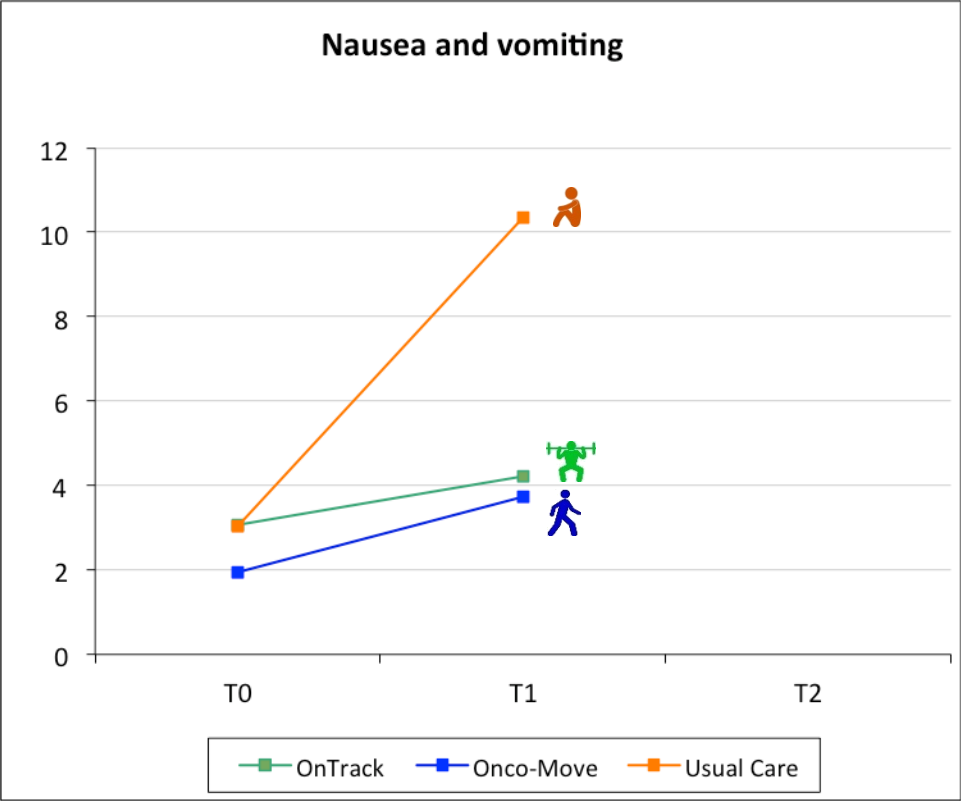
# Fatigue (MFI)





	Mean diff T1	95% CI		ES
 OnTrack  Usual Care	2.7	-4.0	-1.4	0.63
 OncoMove  Usual Care	-1.1	-2.4	0.2	0.28

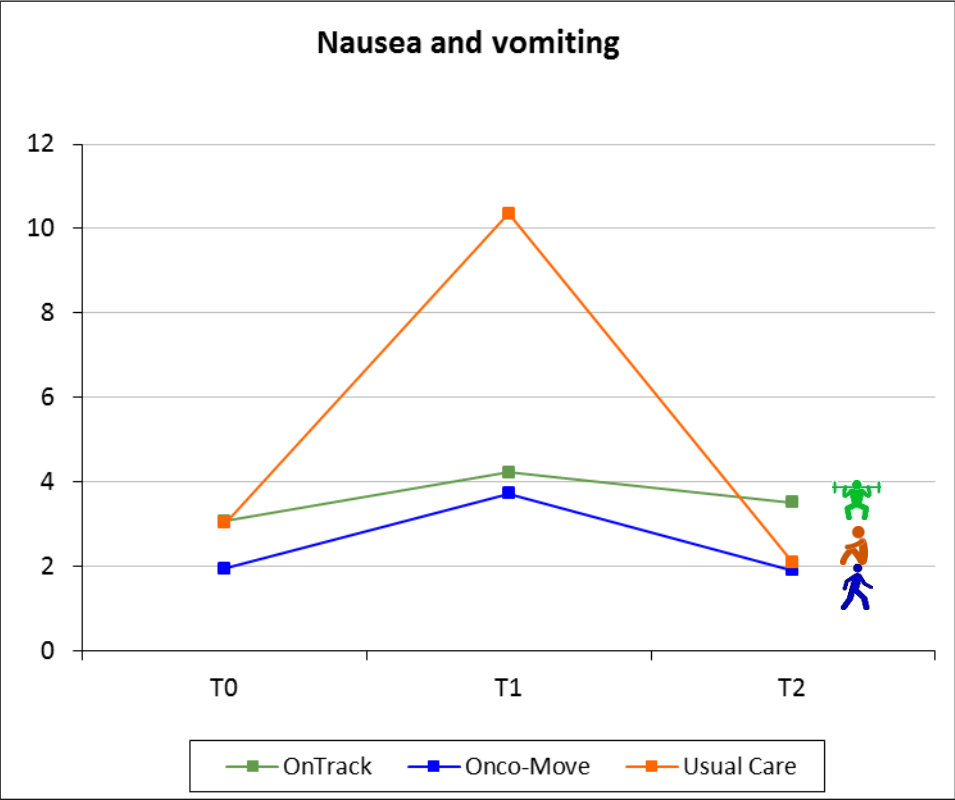
	Mean diff T2	95% CI		ES
 OnTrack  Usual Care	-0.8	-2.6	0.6	0.18
 OncoMove  Usual Care	0.0	-1.3	1.3	0.01





# Emesis







	Mean diff T1	95% CI		ES
 <b>OnTrack Usual Care</b>	-6.2	-11.9	-0.6	0.89
 <b>OncoMove Usual Care</b>	-6.2	-11.9	-0.6	1.00

# Health-related quality of life - Symptoms

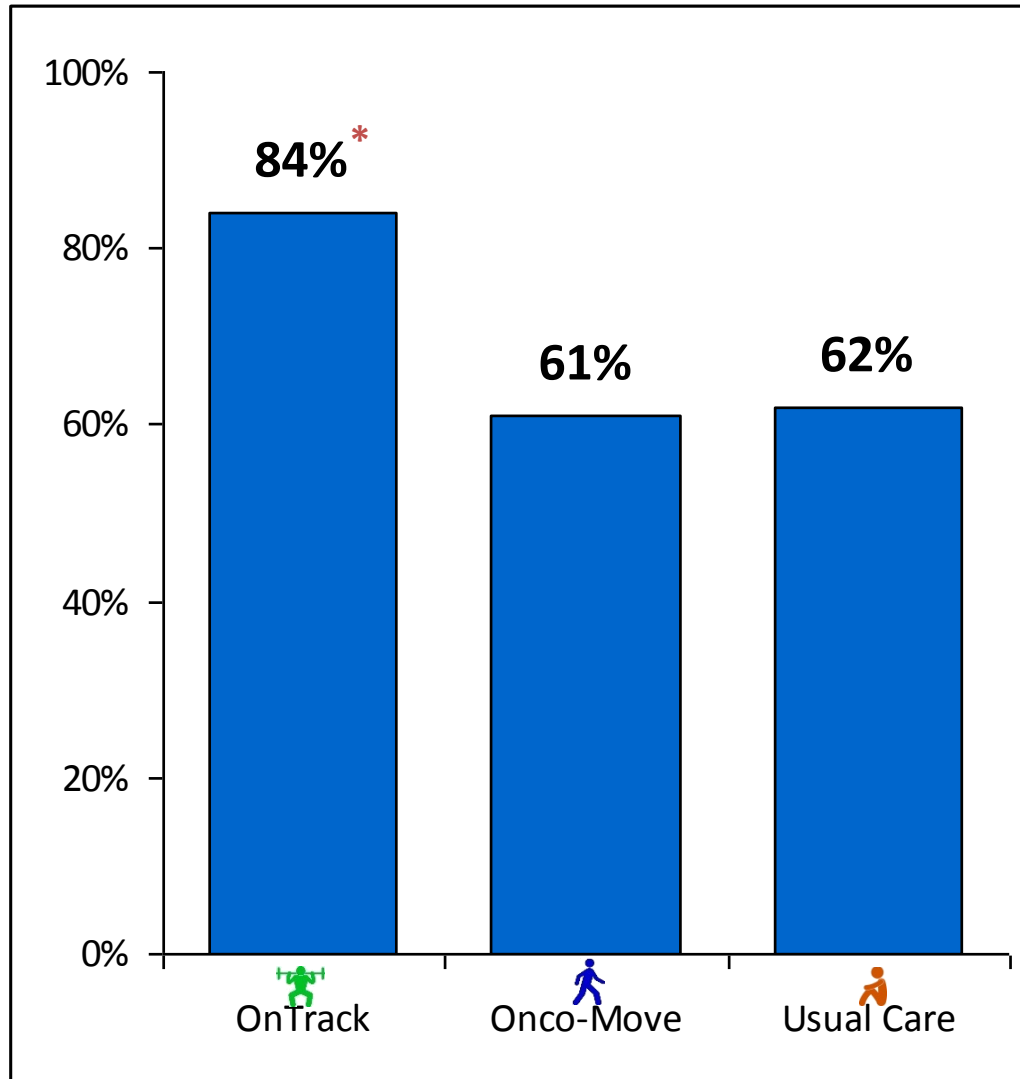


	Mean diff T1	95% CI		ES
 <b>OnTrack</b>  <b>Usual Care</b>	-6.2*	-11.9	-0.6	0.89
 <b>OncoMove</b>  <b>Usual Care</b>	-6.2*	-11.9	-0.6	1.00

	Mean diff T2	95% CI		ES
 <b>OnTrack</b>  <b>Usual Care</b>	1.4	-1.3	4.2	0.21
 <b>OncoMove</b>  <b>Usual Care</b>	0.3	-1.9	2.5	0.04

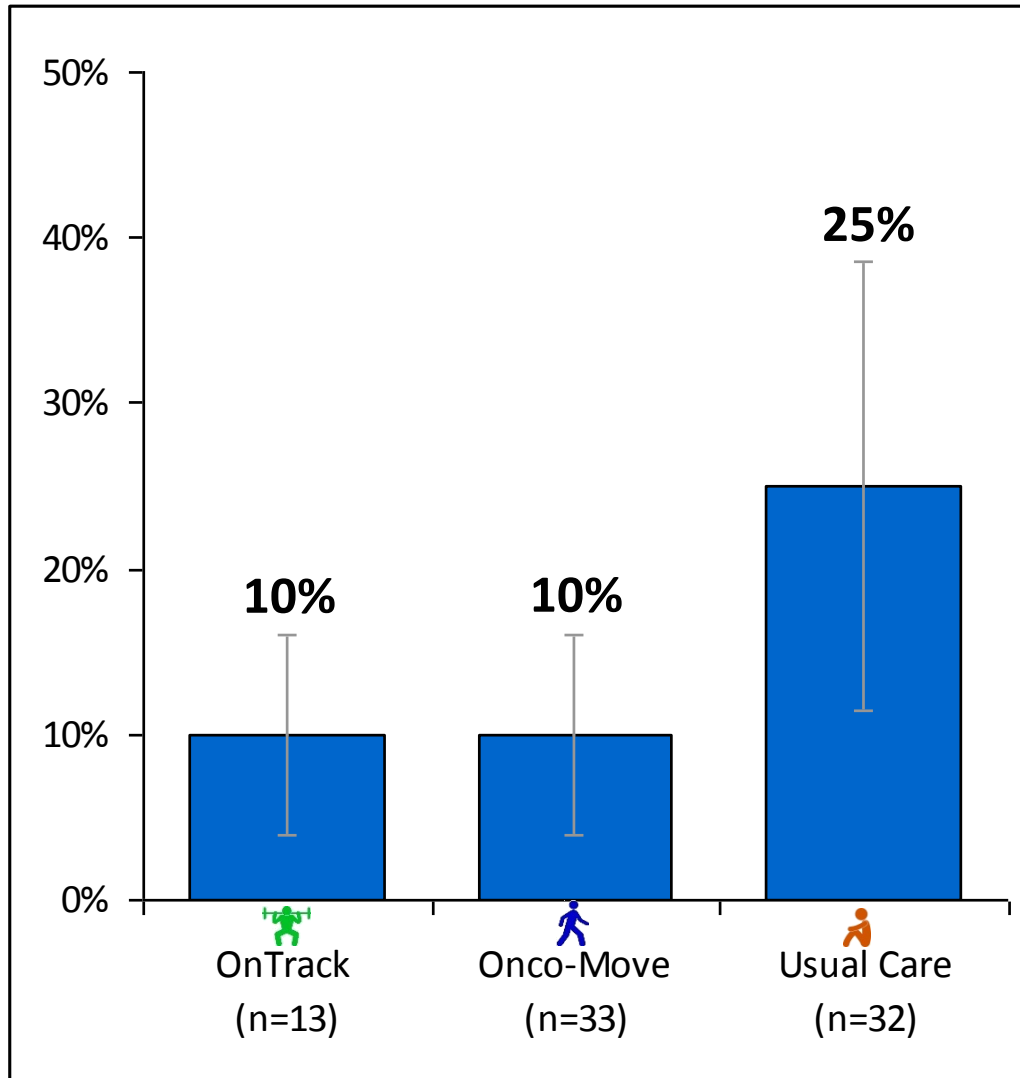
# Chemotherapy completion rates

% of patients who completed entire chemotherapy



# Dose reduction

% dose reduction in patients who had dose adjustments



# Summary of results – OnTrack

**High** intensity **supervised** exercise during chemotherapy results in:

- Maintenance of endurance time
- Maintenance of muscle strength
- Less fatigue
- Less nausea
- Higher chemotherapy completion rates
- Less chemotherapy dose reduction



# Summary of results – Onco-Move

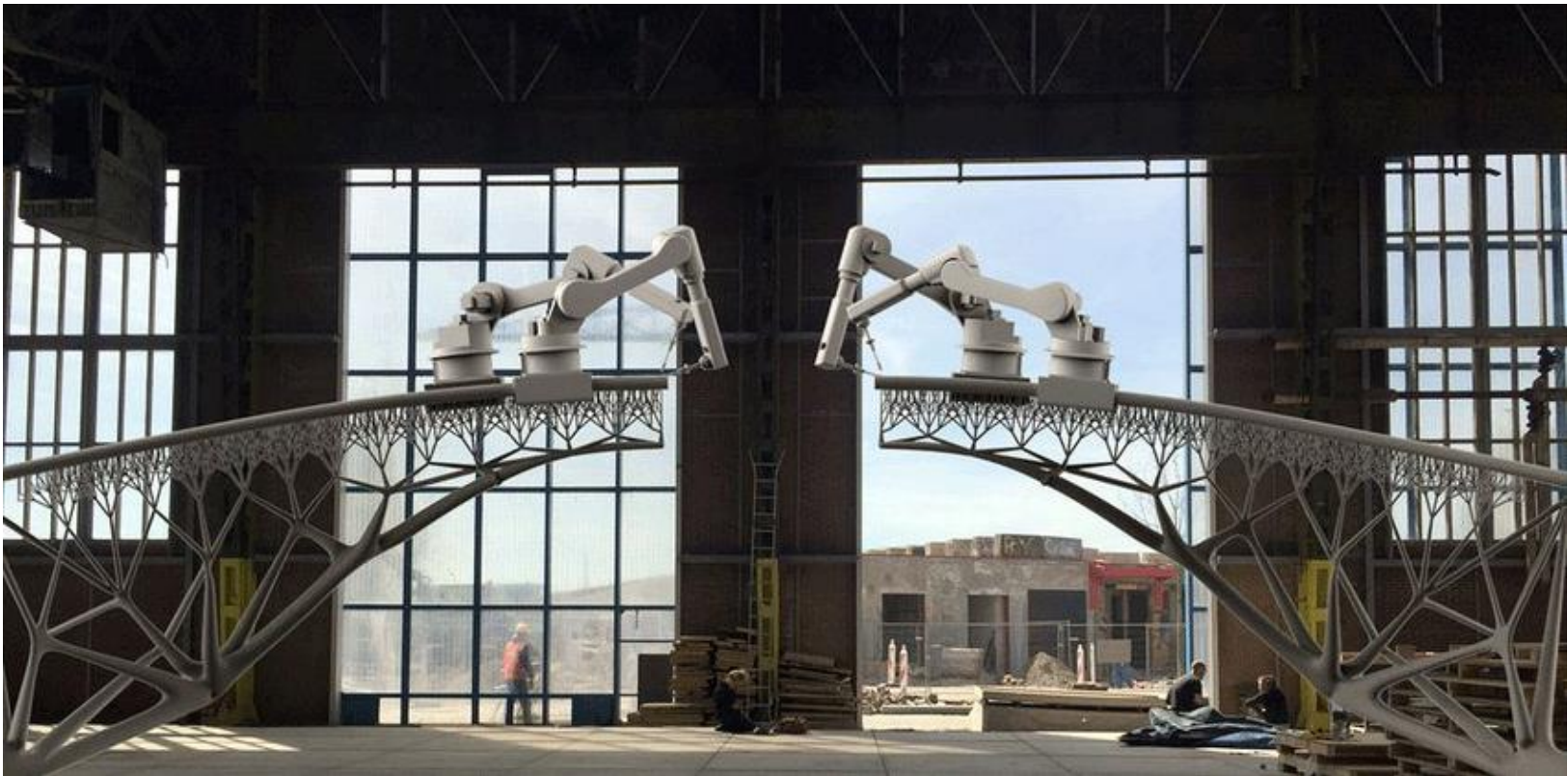
**Low** intensity **home-based** exercise during chemotherapy results in:

- Less decline in endurance time
- Less symptoms: nausea
- Less chemotherapy dose reduction

# Conclusions:

- Breast cancer patients receiving adjuvant chemotherapy benefit from a high intensity exercise program.
- When unable or unwilling to do so, a low intensity exercise program is a reasonable alternative.
- Post-treatment activity and exercise programs are needed to maintain gains in fitness and energy levels
- Long-term follow-up is needed to determine if benefits in terms of chemotherapy completion rates translate into better clinical outcomes (survival benefit)

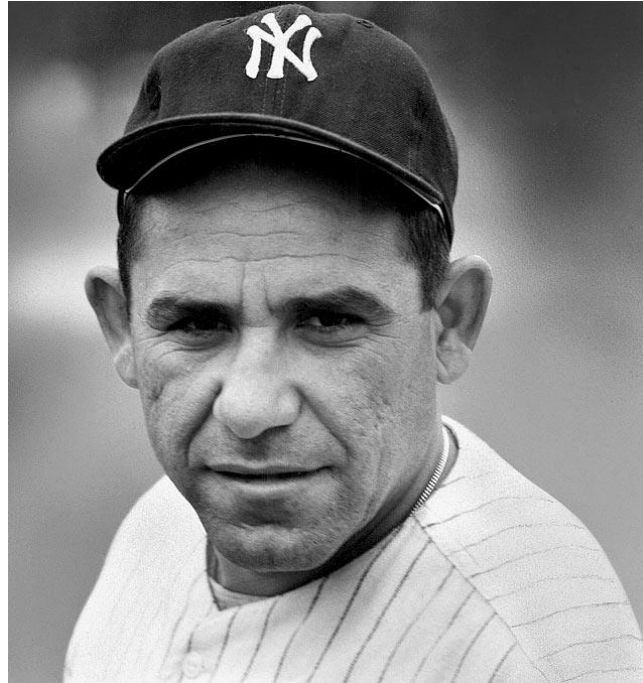
# Bridging the gap between clinical research and practice



JGAURORA, Dutch Start-up Company

# Barriers to implementation of “successful” psychosocial and behavioral interventions

- Attitudinal barriers
- Lack of awareness of available interventions
- Lack of routine screening programs
- Lack of (clear) referral pathways and networks
- Workforce limitations
- Financial barriers (insurance coverage and reimbursement)



Yogi Berra, 1925-2015

“If the world were perfect, it wouldn’t be.”

“The future ain’t what it used to be.”