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Supervised Exercise for Patients With Metastatic Breast Cancer: A Cost-Utility Analysis Alongside the PREFERABLE-EFFECT Randomized Controlled Trial

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DOI https://doi.org/10.1200/JCO-24-01441

ABSTRACT

PURPOSE To evaluate the cost utility of a 9-month supervised exercise program for patients with metastatic breast cancer (mBC), compared with control (usual care, supplemented with general activity advice and an activity tracker). Evidence on the cost-effectiveness of exercise for patients with mBC is essential for implementation in clinical practice and is currently lacking.

METHODS A cost-utility analysis was performed alongside the multinational PREFERABLE-EFFECT randomized controlled trial, conducted in 8 centers across Europe and Australia. Patients with mBC (N = 357) were randomly assigned to either a 9-month, twice-weekly, supervised exercise group (EG) or control group (CG). Costs of the exercise program were calculated through a bottom-up approach. Other health care resource use, productivity losses, and quality of life were collected using country-adapted, self-reported questionnaires. Analyses were conducted from a societal perspective with a time horizon of 9 months. Costs were collected and reported in 2021 Euros (€1 = $1.18 US dollars).

RESULTS Compared with the CG, EG resulted in a quality-adjusted life-year (QALY) gain of 0.013 (95% CI, −0.02 to 0.05) over a 9-month period. The mean costs of the exercise program were €1,696 per patient with one-on-one supervision (scenario 1) and €609 with one-on-four supervision (scenario 2). These costs were offset by savings in health care and productivity costs, resulting in mean total cost differences of −€163 (scenario 1) and −€1,249 (scenario 2) in favor of EG. The probability of supervised exercise being cost-effective was 65% in scenario 1 and 91% in scenario 2 at a willingness-to-pay threshold of €20,000 per QALY.

CONCLUSION Exercise for patients with mBC increases quality of life, decreases costs, and is likely to be cost-effective. Group-based supervision is expected to have even higher cost-savings. Our positive findings can inform reimbursement of supervised exercise interventions for patients with mBC.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

Accepted November 22, 2024
Published January 13, 2025

J Clin Oncol 43:1325-1336

View Online Article

INTRODUCTION

Survival rates are improving for patients with metastatic breast cancer (mBC) because of therapeutic advances.[1-3] Consequently, the focus is shifting toward maintaining health-related quality of life (HR-QoL) and reducing treatment-related side effects.[4] Abundant evidence supports the effectiveness of exercise in achieving these goals in the curative setting.[5,6] However, evidence in the advanced disease setting is scarce. Recently, the multinational PREFERABLE-EFFECT study demonstrated that a 9-month supervised exercise program is also an effective and safe strategy for alleviating fatigue and other burdensome side effects of treatment, and for improving HR-QoL in patients with mBC.[7]

CONTEXT

Key Objective
Is a 9-month supervised exercise program cost-effective compared with control (ie, usual care supplemented with physical activity advice and activity tracker) for patients with metastatic breast cancer (mBC)?

Knowledge Generated
In this multinational randomized clinical trial including 357 patients with mBC, supervised exercise is dominant; quality-adjusted life-years increased by 0.013 (95% CI, −0.02 to 0.05) with cost-savings of €163 ($192 US dollars [USD]; 95% CI, −€1,901 to €2,228) or €1,249 ($1,474 USD; 95% CI, −€817 to €3,315) per patient, when supervised one-on-one or one-on-four, respectively.

Relevance *(S.B. Wheeler)*
These data can inform arguments for reimbursement and scale-up for supportive physical activity interventions for people with cancer, though these programs should be tested in a variety of settings to confirm their cost-benefit.*

*Relevance section written by *JCO* Associate Editor Stephanie B. Wheeler, PhD, MPH.

The global economic costs of mBC are expected to increase from $63.4 billion US dollars (USD) in 2015 to $152.4 billion USD in 2030.[8,9] To keep cancer care affordable, investment in supportive care strategies represents one approach to controlling the cancer burden by reducing disease and treatment-related side effects.[10] Thorough economic evaluations of supportive care strategies are needed to inform decision making.[10] To date, research has focused primarily on the efficacy and effectiveness of exercise in cancer care, while little is known about its cost-effectiveness. Evidence regarding the cost-effectiveness remains inconclusive because of the scarcity and moderate quality of studies, as well as the heterogeneity in the type of exercise delivered and the type of analyses used for the economic evaluation.[11,12] Moreover, to our knowledge, none of the existing studies have included patients with mBC. Hence, we aimed to assess the cost-effectiveness of a 9-month exercise program compared with control (usual care, supplemented with general activity advice and an activity tracker) in patients with mBC alongside the PREFERABLE-EFFECT study.

METHODS

In this economic evaluation alongside the multinational PREFERABLE-EFFECT study,[13] the costs and quality-adjusted life-years (QALYs; Data Supplement, Table S1, online only) of patients with mBC participating in a supervised exercise program were compared with a control group (CG). The evaluation was performed from both a societal perspective and a health care perspective with a 9-month time horizon, matching the intervention period. No discounting was required. Reporting followed the CHEERS 2022 checklist.[14]

PREFERABLE-EFFECT Study

This two-arm randomized controlled trial (RCT) was conducted at eight study centers in Germany (n = 89), the Netherlands (n = 91), Spain (n = 54), Sweden (n = 44), Poland (n = 44), and Australia (n = 35). The study protocol was approved by the institutional review board of the University Medical Center Utrecht, the Netherlands, and by the local ethical review boards of all participating institutions. It was registered at ClinicalTrials.gov (identifier: NCT04120298). After providing written informed consent, patients with mBC with a life expectancy of ≥6 months and without unstable bone metastases were randomly assigned (stratified by study center and therapy line) to a supervised exercise intervention (exercise group) or to the control group. Both groups received usual care and an activity tracker. CG received written information on physical activity guidelines (ie, 150 minutes of aerobic exercise and two-three sessions of resistance exercise per week). The exercise group (EG) received a 9-month multimodal exercise program, which included resistance, aerobic, and balance exercises, and consisted of twice-weekly supervised exercise sessions of 1 hour for the first 6 months. For the last 3 months, 1 weekly supervised session was replaced by an unsupervised session to facilitate the transition to self-directed exercise after 9 months. Supervision was provided by qualified exercise professionals (Data Supplement, Table S2).

Recently, the results for the primary end points of the RCT were published.[7] Between 2020 and 2022, 357 patients were enrolled and randomly assigned into EG (n = 178) or CG (n = 179; Fig 1). Mean age of the participants was 55.4 years (SD = 11.1), the majority were female (99.4%), 44.8% had a paid job, was receiving first/second line of treatment (74.8%), and had bone metastases (67.2%; Data Supplement, Table S3).

Data Collection

The validated (across different populations, settings, and disease conditions, including breast cancer [BC]) EuroQol 5-

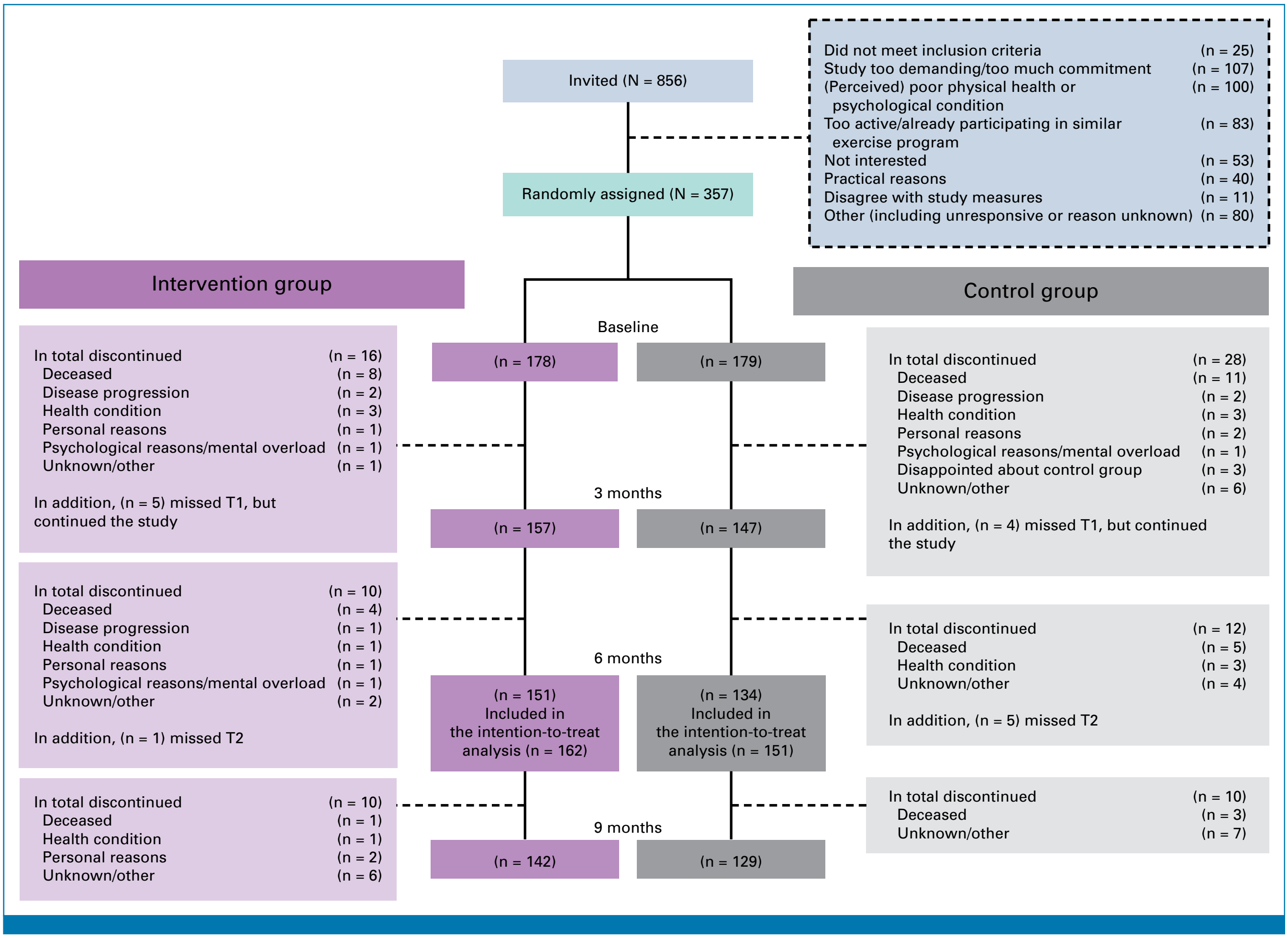

FIG 1. CONSORT diagram. Flow of participants through the study.

dimension questionnaire (EQ-5D-5L),[15-17] iMTA Medical Consumption Questionnaire (iMCQ), and iMTA Productivity Cost Questionnaire (iPCQ) were completed by participants at baseline (only EQ-5D-5L), and 3, 6, and 9 months. The exercise intervention costs were calculated using a bottom-up method (Data Supplement, Table S1). Data on costs were collected and reported in 2021 Euros (average 2021 exchange rate: €1 = $1.18 USD).

Resource Use and Costs

Supervised Exercise Program

Centers where the exercise program was performed completed a data collection sheet documenting personnel and equipment costs (Data Supplement, Table S4). Details on facility rent were insufficient to calculate overhead. Therefore, overhead costs (ie, capital overhead, management, and other noncare staff) were estimated to be 44%, on the basis of estimations in the Unit Costs of Health and Social Care 2022 manual of the UK and Dutch guidelines for health economic evaluations.[18,19] Group sizes per exercise session differed per country, ranging from one to five participants (Data Supplement, Table S2). For the purpose of informing decision making on implementing exercise in clinical practice, we considered two scenarios for group size: (1) one-on-one supervision and (2) one-on-four supervision. We included the one-on-one scenario to examine cost-effectiveness in settings where larger group sizes are not feasible (eg, regions with low population density), and we consider the one-on-four scenario to reflect clinical practice since most participants exercised in groups. We assumed that group size would not affect the quality of the session and, thus, not affect QALYs. The number of exercise sessions per participant was derived from attendance logs, with a cutoff value of 60 sessions (ie, the maximum number of sessions offered during the study). Costs were estimated per participant, with country-specific wages obtained from each participating center. Costs of the activity tracker (€75) were added for each participant in both EG and CG.

Other Health Care Resource Use

Health care consumption was measured using an adjusted version of the iMCQ,[20] and included information on hospital resource use (eg, hospitalizations, outpatient visits, and emergency visits) and extramural care (eg, general practitioner visits, physiotherapy for reasons other than the exercise program, and home and informal care). More information on how costs were calculated can be found in the Data Supplement (Methods S1 and Table S5).

In the Netherlands, exercise sessions were supervised by a physiotherapist. If participants reported exercise sessions as physiotherapy visits, the number of physiotherapy visits was set to 0 (n = 13 participants). For home and informal care, responses were capped at 16 hours/day.[21] Other extreme values were checked by either contacting the participant or checking the participant's medical record.

Indirect Costs

Productivity losses of paid work, including short-term absenteeism, long-term absenteeism, and presenteeism, were measured using the iPCQ.[22] Labor costs were estimated using country-specific hourly compensation of employees.[23] More information on how costs were calculated can be found in the Data Supplement (Methods S1 and Table S6).

Quality-Adjusted Life-Years

QALYs were estimated by combining utility values from the EQ-5D-5L with mortality data. Utility scores represent HR-QoL, in which 0 corresponds to death and 1 corresponds to perfect health. A single value set was applied to estimate utility scores.[24] The German value set[25] was chosen as a high number of participants are German and the mean utility score fell between the mean scores of the other value sets. If a participant died, utility scores were zero from their date of death. The QALYs over 9 months were calculated using an AUC approach with linear interpolation (Data Supplement, Table S1).[26]

Cost-Utility Analysis

Statistical analysis was performed with R (R Foundation for Statistical Computing), version 4.3.1. In total, 12%, 14%, and 15% of responses were missing for the iMCQ and the EQ-5D-5L at 3, 6, and 9 months, respectively, and 16%, 20%, and 22% for the iPCQ, excluding missing values due to death. Missing data were handled with multiple imputation (m = 10), using the R MICE-package (Data Supplement, Table S7).[27,28] Bootstrapping (5,000 iterations) was used to estimate outcome uncertainty.[28] Two seemingly unrelated regressions[28] were used to estimate incremental costs and QALYs, adjusted for stratification factors. Incremental QALYs were additionally adjusted for baseline utility score. Effect sizes (ES) were calculated using Cohen's d-statistic.[29] Cost-effectiveness planes (CE-plane) and cost-effectiveness acceptability curves (CEAC) were constructed. The probability of cost-effectiveness was estimated for the upper and lower limits of the willingness-to-pay thresholds (WTP) of the Netherlands (€20,000 and €80,000/QALY), which encompass the thresholds used by other countries.[30-33]

The two base case analyses (Data Supplement, Table S1) were (1) one-on-one supervision, societal perspective; and (2) one-on-four supervision, societal perspective. Three scenario analyses (Data Supplement, Table S1) were included: (1) one-on-one supervision, health care perspective; (2) one-on-four supervision, health care perspective; and (3) supervision using group size in the trial, societal perspective. The health care perspective excludes costs related to productivity losses and informal care. Additional scenario analyses where all participants were considered Dutch (unit costs and EQ-5D-5L value set) can be found in the Data Supplement (Table S8). Analyses were performed according to the intention-to-treat principle and Dutch guidelines of health economic evaluations.[19,34]

RESULTS

Costs

The mean 9-month costs of the exercise program per participant were €1,696 when supervised one-on-one, and €609 when supervised one-on-four (Table 1) for an average of 40.5 sessions. Session costs can be found in the Data Supplement (Table S9).

Compared with CG, mean health care costs over 9 months were lower in EG for home care (€93 *v* €468), day treatments (€2,105 *v* €2,437), and hospital visits (€1,097 *v* €1,311). For EG, higher mean costs were found for physiotherapy (€294 *v* €241). Violin plots showed an outlier for home care in CG, but similar distributions for other costs (Data Supplement, Fig S1). Throughout the study, working hours decreased in both groups (Table 2). Productivity costs for short-term absenteeism were lower in EG compared with control (€1,202 *v* €1,637).

Total costs were €9,700 for CG and €9,568 for EG when supervised one-on-one (adjusted difference: −€163), and €8,482 for EG when supervised one-on-four (adjusted difference: −€1,249). Country-specific resource use can be found in the Data Supplement (Table S10-S15).

Quality of Life

Compared with CG, EG had higher utility values at baseline, and at 3, 6, and 9 months (mean between-group difference 0.016 [95% CI, −0.010 to 0.042, ES = 0.13], 0.020 [95% CI, −0.034 to 0.074, ES = 0.16], 0.048 [95% CI, −0.016 to 0.112, ES = 0.39], and 0.029 [95% CI, −0.049 to 0.106, ES = 0.23], respectively; Table 3). Mean utility values decreased over the 9-month intervention period for both CG and EG, from 0.871 to 0.715 in CG and 0.887 to 0.744 in EG. Mean (SE) QALYs after 9 months, adjusted for baseline utility scores, were 0.606 (0.011) in EG and 0.591 (0.012) in CG (difference = 0.013 QALY [95% CI, -0.017 to 0.046]). This corresponds to an additional 5 days in perfect health over 9 months in favor of EG.

TABLE 1. Costs (€, 2021) After Multiple Imputation for EG and CG Over 9 Months

	EG (n = 178)			CG (n = 179)			
Cost	People, No.[a]	HCU, Mean No.[b]	Mean Cost	People, No.[a]	HCU, Mean No.[b]	Mean Cost	Mean Cost Difference[c]
Intervention costs							
Scenario one-on-one[c]	162	40.5 visits	€1,771	179	0 visits	€75	€1,696
Scenario one-on-four[d]	162	40.5 visits	€684	179	0 visits	€75	€609
Direct health care costs							
GP	152	5.6 visits	€182	151	5.8 visits	€192	−€10
Physiotherapy	110	10.1 visits	€294	115	7.7 visits	€241	€53
Dietician	51	0.5 visits	€12	55	0.6 visits	€16	−€4
Social worker	53	0.6 visits	€41	57	0.5 visits	€32	€9
Psychologist	77	2.4 visits	€221	87	2.6 visits	€228	−€7
Occupational therapy	26	0.4 visits	€13	46	0.5 visits	€17	−€4
Acupuncture	63	1.2 visits	€73	71	1.8 visits	€111	−€38
Hospital							
Hospital admissions	62	1.8 days	€1,097	64	2.3 days	€1,311	−€214
Outpatient visits	168	8.9 visits	€1,151	169	10.1 visits	€1,311	−€160
Day treatments	145	7.5 visits	€2,105	155	8.8 visits	€2,437	−€332
A&E	53	0.4 visits	€101	75	0.5 visits	€143	−€42
Other							
Home care	29	4.1 hours	€93	43	17.2 hours	€468	−€375
Total direct health care costs		€5,363			€6,485	−€1,122	
Indirect health care costs							
Informal care	86	57.0 hours	€736	108	79.6 hours	€961	−€225
Indirect non–health care costs							
Temporary absenteeism	55	36.4 hours	€1,202	65	53.0 hours	€1,637	−€435
Long-term absenteeism	20	11.7 hours	€344	23	11.1 hours	€351	−€7
Presenteeism	47	4.7 hours	€131	71	5.8 hours	€168	−€37
Total costs							
Scenario one-on-one[d]	178	—	€9,568	179	—	€9,700	−€132
Scenario one-on-four[e]	178	—	€8,482	179	—	€9,700	−€1,218

Abbreviations: A&E, accidents and emergency; CG, control group; EG, exercise group; GP, general practitioner; HCU, health care usage.
[a]Number of participants with an average health care usage >0 after multiple imputation.
[b]Average health care usage of all participants, including those who indicated 0 visits/days/hours.
[c]Unadjusted for treatment center and line of treatment.
[d]One-on-one, with supervision for 75% of the exercise session.
[e]One-on-four, with supervision during the entire exercise session (100%).

TABLE 2. Productivity Costs After Multiple Imputation for EG and CG Over 9 Months

	EG (n = 178)			CG (n = 179)			
Productivity Cost Category	People, No.[a]	Mean Hours[b]	Mean Cost	People, No.[a]	Mean Hours[b]	Mean Cost	Mean Cost Difference
Participants with paid job, No.							
3 months	76	118.9	—	82	112.9	—	—
6 months	74	119.9	—	78	108.4	—	—
9 months	68	104.3	—	69	97.7	—	—
Long-term absenteeism							
3 months	10	6.3	€174	6	4.6	€155	€19
6 months	5	1.2	€41	3	4.2	€115	−€74
9 months	4	1.9	€38	0	0.0	€0	€38
Short-term absenteeism							
3 months	31	17.6	€586	33	18.2	€532	€54
6 months	18	5.9	€194	36	19.0	€591	−€397
9 months	23	12.8	€422	28	15.9	€514	−€92
Presenteeism							
3 months	30	1.5	€45	34	2.9	€79	−€34
6 months	15	2.0	€59	44	1.5	€46	€13
9 months	20	1.3	€28	32	1.4	€43	−€15

NOTE. Country-specific friction period is applied (Data Supplement, Table S5).
Abbreviation: EG, exercise group.
[a]Number of participants with an average health care usage >0 after multiple imputation.
[b]Average hours of all patients over 3-month period, including participants who indicated 0 hours.

Cost-Utility Analyses

The results of the cost-utility base case and scenario analyses are presented in Table 4. Both base case analyses (one-on-one and one-on-four supervision) showed cost-savings (probability of 54% and 88%, respectively) and increased QALYs (probability of 79% for both scenarios) for EG and are, therefore, considered dominant (ie, the intervention is more effective and less costly; Data Supplement, Table S1) compared with CG. The CE-plane showed that with one-on-one supervision, 44% of the cost-effect pairs were in the southeast quadrant, representing cost-savings and higher effectiveness of the exercise program, and 35% were in the northeast (NE) quadrant, representing higher costs and higher effectiveness (Table 4 and Fig 2A). With one-on-four supervision, 70% were in the southeast quadrant and 9% in the NE quadrant. The CEAC indicated that the probability of one-on-one supervised exercise being cost-effective compared with control was 65% and 77% when the WTP-threshold was set at €20,000 and €80,000/QALY (Fig 2A), respectively, and 91% and 92% for one-on-four supervision (Fig 2B).

Scenario Analyses

The scenario analysis with one-on-four supervision from a health care perspective was dominant compared with CG (Table 4); one-on-one supervision from a health care

TABLE 3. Effects of the EFFECT Exercise Program on Utilities and QALYs

Effect	EG (n = 178), Mean (SE)	CG (n = 179), Mean (SE)	Mean Between-Group Difference, 95% CI	ES
Utility at baseline	0.887 (0.008)	0.871 (0.010)	0.016 (−0.010 to 0.042)	0.13
Utility at 3 months	0.837 (0.019)	0.816 (0.020)	0.020 (−0.034 to 0.074)	0.16
Utility at 6 months	0.797 (0.020)	0.749 (0.026)	0.048 (−0.016 to 0.112)	0.39
Utility at 9 months	0.744 (0.027)	0.715 (0.027)	0.029 (−0.049 to 0.106)	0.23
QALY, unadjusted	0.610 (0.012)	0.587 (0.013)	0.024 (−0.014 to 0.061)	—
QALY, adjusted[a]	0.606 (0.011)	0.591 (0.012)	0.013 (−0.019 to 0.046)	—

NOTE. Suggested interpretation by Cohen: ES <0.2, no difference; ES of 0.2-0.5, small difference; ES of 0.5-0.8, medium difference; and ES 0.8 or more, large difference.
Abbreviations: CG, control group; EG, exercise group; ES, Cohen's effect size; QALY, quality-adjusted life-year.
[a]Adjusted for baseline utility, treatment center, and line of treatment.

TABLE 4. Results of the Cost-Utility Scenario Analyses

									CE Plane[a]			
Type of Analysis		Mean Cost (SE)	ΔC	95% CI	Mean QALY (SE)	ΔE	95% CI	ICER	NE	SE	SW	NW
Base case analyses	One-on-one group size, societal perspective											
	EG	€9,553 (€652)	−€163	−€2,228 to €1,901	0.61 (0.01)	0.01	−0.02 to 0.05	Dominant	35%	44%	12%	10%
	CG	€9,716 (€862)		Reference	0.59 (0.01)		Reference					
	One-on-four group size, societal perspective											
	EG	€8,467 (€649)	−€1,249	−€3,315 to €817	0.61 (0.01)	0.01	−0.02 to 0.05	Dominant	9%	70%	18%	3%
	CG	€9,716 (€863)		Reference	0.59 (0.01)		Reference					
Scenario analyses	One-on-one group size, health care perspective											
	EG	€7,142 (€403)	€548	−€909 to €2,004	0.61 (0.01)	0.01	−0.02 to 0.05	€40,723	61%	18%	5%	16%
	CG	€6,594 (€626)		Reference	0.59 (0.01)		Reference					
	One-on-four group size, health care perspective											
	EG	€6,056 (€397)	−€538	−€1,990 to €915	0.61 (0.01)	0.01	−0.02 to 0.05	Dominant	18%	61%	16%	5%
	CG	€6,594 (€626)		Reference	0.59 (0.01)		Reference					
	Trial-based group size, societal perspective											
	EG	€8,959 (€652)	−€756	−€1,827 to €1,315	0.61 (0.01)	0.01	−0.02 to 0.05	Dominant	18%	61%	15%	5%
	CG	€9,716 (€864)		Reference	0.59 (0.01)		Reference					

NOTE. CI estimated using the nonparametric bootstrap (bias-corrected intervals).

Abbreviations: ΔC, difference in costs over the 9-month intervention period (EG−CG, 2021 €); ΔE, difference in effect over the 9-month intervention period (EG−CG, QALYs); CE, plane, cost-effectiveness plane; CG, control group; EG, exercise group; ICER, incremental cost-effectiveness ratio; NE, northeast quadrant; NW, northwest quadrant; QALY, quality-adjusted life-year; SE, southeast quadrant; SW, southwest quadrant.

[a]Percentages might not add up to 100% because of rounding.

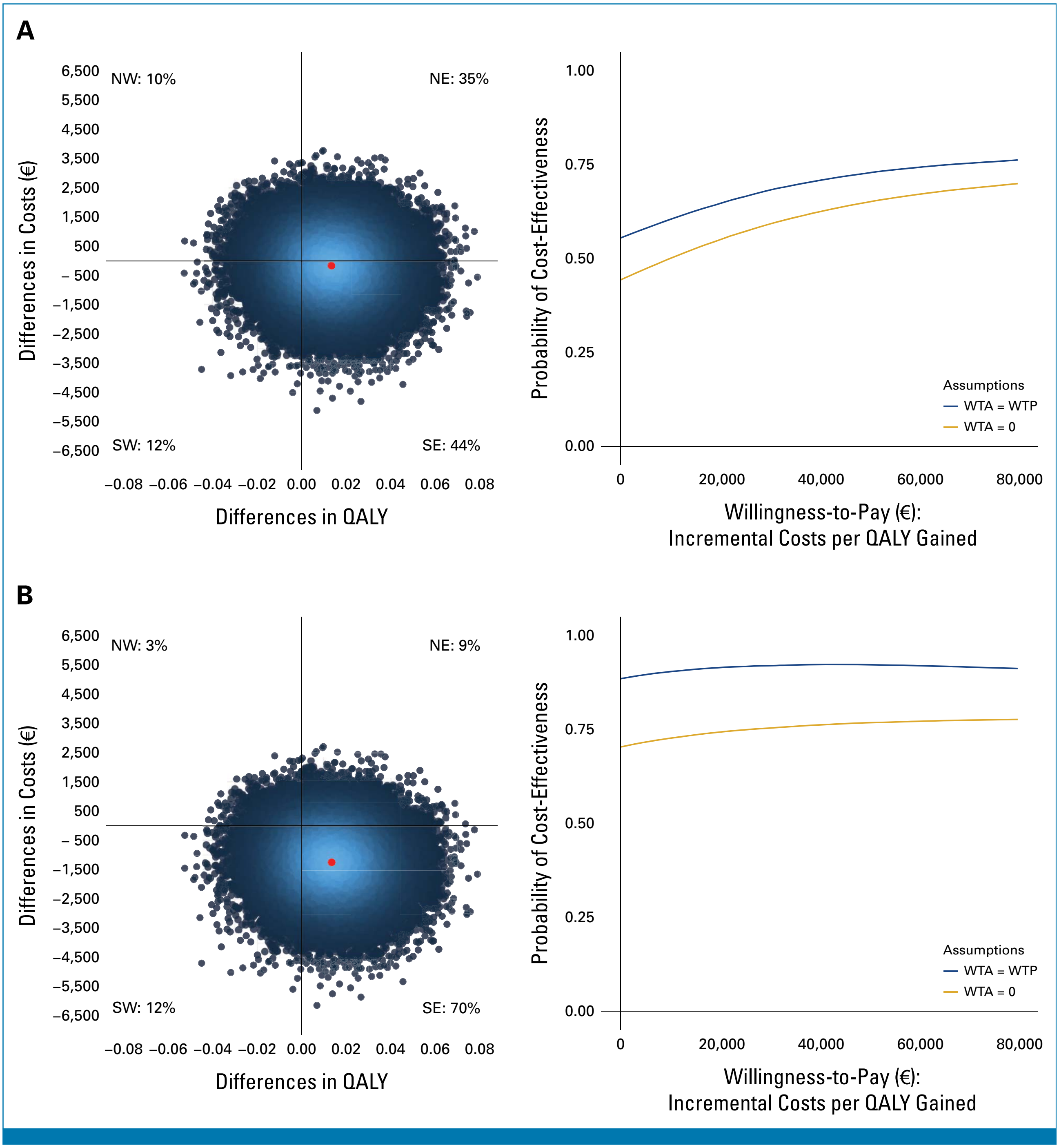

FIG 2. Cost-effectiveness plane (left) and cost-effectiveness acceptability curve (right) for (A) one-on-one supervision and (B) one-on-four supervision. WTA = WTP: points in the southwest quadrant are included if (difference in costs/difference in QALY) > WTP. WTA = 0: points in the southwest quadrant are excluded. The cost-effectiveness plane displays the difference in costs (vertical axis) and difference in QALY (QALYs, horizontal axis) between the intervention (EG; 9-month exercise program) and CG after 5,000 bootstrap iterations. Every dot indicates the difference in costs and QALYs (ie, a cost-effect pair) between EG and CG of one bootstrap iteration, thus representing the uncertainty of the analysis. The red dot indicates the difference in costs and QALYs between EG and CG before bootstrapping, while the shades of blue represent the density of bootstrap iterations (lighter = higher density). The percentage of bootstrap iterations per quadrant is displayed in the figures and Table 4. If the cost-effect pair falls within the NW or southeast quadrant, the choice between EG and CG is clear. In the southeast quadrant, EG is more effective and less costly compared with CG, and therefore dominates CG. In the NW quadrant, the opposite is true. In the SW and NE quadrants, the choice depends on the maximum cost-effectiveness ratio one is willing to accept. The cost-effectiveness acceptability curve displays the probability of cost-effectiveness of EG for every WTP threshold. This probability is based on the number of bootstrap iterations that are considered cost-effective at a certain threshold (ie, either lower costs and higher effectiveness for EG, or higher costs and higher effectiveness, whereby the costs per QALY gained are lower than the WTP threshold). The higher the WTP threshold, the higher the probability of cost-effectiveness. The primary one-on-four scenario (continued on following page)

FIG 2. (Continued). is cost-effective at lower WTP thresholds than the one-on-one scenario. CG, control group; EG, exercise group; NE, northeast quadrant; NW, northwest quadrant; QALY, quality-adjusted life-year; SE, southeast quadrant; SW, southwest quadrant; WTA, willingness-to-accept (willingness to accept lower QALYs if it comes with lower costs); WTP, willingness-to-pay (willingness to pay for additional QALYs).

perspective resulted in incremental costs of €548, with a probability of cost-effectiveness of 36% and 63% at a WTP threshold of €20,000 and €80,000/QALY, respectively (Data Supplement, Fig S2). When assuming that the exercise program would be implemented using the group size as applied in the trial (ranging from one to five participants per session, depending on the country), the cost-savings from a societal perspective were €756 (ie, between the cost-savings observed for the two base case analyses). The results of the additional scenario analyses, conducted from a societal perspective and assuming all patients were Dutch (Data Supplement, Table S8), were similar to the base case analyses.

DISCUSSION

Supervised exercise for patients with mBC is dominant compared with CG, thus resulting in an increase in QALYs at similar or lower costs. Although the mean exercise program costs were €1,696 over 9 months when supervised one-on-one and €609 when supervised one-on-four, these costs were offset by savings in health care and productivity costs. Hence, supervised exercise for patients with mBC has a 65%-91% probability to be cost-effective at a WTP threshold of €20,000/QALY.

To the best of our knowledge, the current study is the first economic evaluation of supervised exercise in patients with mBC. Other RCTs (n = 4) have investigated the cost-effectiveness of supervised exercise in patients with BC receiving curative treatment and applied different exercise interventions. In line with our study, van Waart et al[35] found that a moderate- to high-intensity supervised exercise program could be considered cost-effective (WTP = €80,000/QALY: 79% *v* 77% in our study) compared with usual care. In the other three RCTs, the probability of exercise being cost-effective was low.[36-38] These studies involved either a lower intensity or shorter exercise program compared with PREFERABLE-EFFECT, had no or large group-based (n = 8 participants) supervision, or a different comparator (ie, relaxation and flexibility program or personalized dietary and physical activity counseling), which might explain the divergent findings.

Our findings indicate that the largest cost-savings occurred in home care, productivity losses, day treatments, and hospital admissions. Importantly, savings were found for short-term absenteeism, which suggests higher productivity because of better health. This is in line with earlier findings on favorable effects of exercise on clinically relevant outcomes, including fatigue, pain, dyspnea, physical fitness, physical functioning, role functioning, and social functioning.[7] This suggests that participants in EG were better able to engage in activities of daily living with less impact from their disease and treatment. Previous observational studies have shown that lower symptom burden and better physical functioning positively affect health care use and productivity.[39,40] In the abovementioned studies in early BC, no overall cost-savings were found. For some cost categories, smaller cost-savings were observed, and van Waart et al also found cost-savings for home care.[35-38]

In PREFERABLE-EFFECT, beneficial effects of exercise on disease-specific HR-QoL and physical fatigue were found for patients with mBC, measured using the EORTC QLQ-C30 and EORTC-FA12, respectively.[7] In this economic evaluation, the EQ-5D-5L was used to assess HR-QoL. No significant differences were found between groups, but the study was also not powered to this outcome. Utility scores were higher for EG at all time points, resulting in an adjusted QALY difference corresponding to 5 days in perfect health in favor of EG. Although fatigue affects EQ-5D-5L utility scores,[41,42] this generic questionnaire is not designed to capture the specific impact of changes in cancer-related fatigue on HR-QoL.[43,44] Finally, as suggested by a recent systematic review, cost-effectiveness might be higher with a longer time horizon than the 9 months of the PREFERABLE-EFFECT trial.[12] Since long-term effects of the exercise program on the prognosis of our study population are uncertain, we cannot draw inferences on long-term health economic effects.

Cost-effectiveness, in addition to clinical outcomes, are essential to make informed decisions on implementation of individually or group-based supervised exercise interventions. In this study, EG size varied, but was kept constant in the two base case analyses, assuming group size does not affect QALYs. Research suggests that supervised group-based exercise might have a stronger positive effect on HR-QoL compared with individual supervision, while exercise effects on fatigue and physical fitness are similar.[45-47] Regardless, the analyses indicate that both individually and group-based supervised exercise are cost-effective compared with control, with group-based exercise having larger cost-savings. These findings support expanding the existing ACSM[5] and ASCO[6] guidelines, which advocate for the integration of exercise as an integral component of supportive care for patients during and after curative cancer treatment, to include patients with mBC.

Strengths of this study are its multinational, randomized, and pragmatic design with a relatively large sample size. Pragmatic trials better reflect daily conditions, making them more suitable for clinical and policy decision making.

Limitations of our study are that participants were not blinded to group assignment because of the nature of the intervention, potentially leading to an underestimation of the intervention effect as control participants might have increased their physical activity levels. Since CG only increased their light- and moderate-intensity physical activities (data shown in the study by Hiensch et al[7]), knowledge of group assignment was assumed to have had minimal impact on observed effects. Although efforts were made to collect country-specific unit costs to better reflect absolute and relative price differences, variation in methodology contribute substantially to differences in unit costs.[48] Therefore, only the results of the medical basket approach have been presented. Further research is needed to determine the impact of country-specific unit costs and variations in methodology on the outcomes of cost-effectiveness results. The impact of varying unit costs was assessed by including a scenario from the Dutch perspective (Data Supplement, Table S8), which showed similar cost-effectiveness outcomes. Finally, the estimated overhead costs might not fully capture the variability in overhead costs across different settings (eg, within and outside hospital setting, urban *v* rural facilities, private *v* public facilities, or differences across health care systems). Therefore, actual overhead costs may vary.

In conclusion, to our knowledge, this multinational study is the first to show that for patients with mBC, supervised exercise is associated with higher QALYs and similar costs or cost-savings compared with control. The additional costs of the exercise program are offset by a reduction in health care resource use and productivity losses. Both individually supervised and group-based supervised interventions are cost-effective, with the latter showing dominance because of higher cost-savings. These findings can inform reimbursement of exercise supervised by an exercise specialist as part of standard clinical care for patients with mBC. If group-based exercise is not feasible, our results indicate that individually supervised exercise programs also represent a cost-effective option compared with control.

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PRIOR PRESENTATION

Presented in part at the 2024 ASCO Annual Meeting, Chicago, IL, May 31-June 4, 2024.

SUPPORT

Supported by the European Union's Horizon 2020 research and innovation program (No. 825677) and the National Health and Medical Research Council of Australia (2018/GNT1170698).

CLINICAL TRIAL INFORMATION

NCT04120298

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-01441.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-24-01441.

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ACKNOWLEDGMENT

The authors thank all participants, all involved exercise professionals, and all professional staff at all participating centers in Germany (Heidelberg University Hospital/German Cancer Research Center [DKFZ]/National Center for Tumor Diseases [NCT] Heidelberg, and German Sport University Cologne [DSHS]), the Netherlands (University Medical Center Utrecht [UMCU], the Netherlands Cancer Institute [NKI], Diakonessenhuis Utrecht, Alexander Monro Ziekenhuis), Poland (Greater Poland Cancer Center [GPCC]), Spain (Onkologikoa [ONK]), Sweden (Karolinska Institutet [KI] and Karolinska University Hospital), and Australia (Australian Catholic University [ACU], Peter MacCallum Cancer Center, Royal Melbourne Hospital, Cabrini Health) for their invaluable participation in this trial. We also thank our project partner the European Breast Cancer Coalition Europa Donna for their contribution to the PREFERABLE-EFFECT randomized controlled trial.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Supervised Exercise for Patients With Metastatic Breast Cancer: A Cost-Utility Analysis Alongside the PREFERABLE-EFFECT Randomized Controlled Trial

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.