PREFERABLE

# Recommendations for implementation of exercise for patients with metastatic breast cancer

## based on results of the PREFERABLE project

Recommendations presented in this document are based on a study funded by the European Commission Research & Innovation Horizon 2020 program under grant agreement No. 825677.

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DELIVERABLE 9.7 of the PREFERABLE project

June 2024

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**Acknowledgement**

We thank all participants, clinical and research staff for their support in conducting the studies within the PREFERABLE project, which led to the development of the recommendations presented in this document. We thank the EU officer Ioannis Vouldis for supporting the project.

**Disclaimer**

The information in this document is based on the scientific findings from the EU funded PREFERABLE project (No. 825677). Several of the recommendations in this document have been published before in Deliverable 3.3 of that project, based on the PREFERABLE PERSPECTIVE sub study. For the current report, these recommendations have been updated, using the results obtained in PREFERABLE EFFECT and additional work packages. In case of any discrepancies the recommendations as formulated here should be used.

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**Conflicts of interest**

The authors declare no conflicts of interest.

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# 1 PREAMBULE

Exercise has shown to be effective to reduce many side effects, including fatigue, for people during or after cancer treatment with intent to cure. The evidence regarding the effectiveness for people with advanced stages of cancer was inconclusive. The PREFERABLE project aimed to strengthen the evidence base in this clinical context, through conducting a full-scale randomized controlled trial of exercise for people with metastatic breast cancer (MBC) to reduce fatigue and improve quality of life (EFFECT) and by conducting a social sciences study to explore the perspective of patients with MBC about their perceived barriers, facilitators, values and outcome expectations (PERSPECTIVE) and by exploring the perspectives of other stakeholders including health care insurers, policy makers and health care providers and exercise professionals.

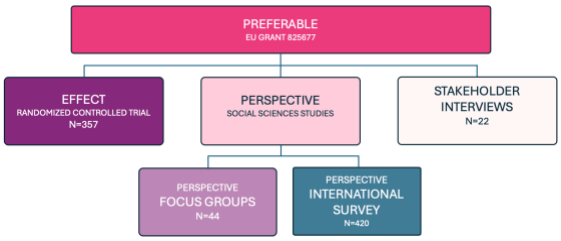


Figure 1 – Structure of the PREFERABLE project

Results of the PREFERABLE project have and will be published in several scientific papers. Current publications are at the end of the document. Here, we summarize the main findings and provide recommendations about integrating exercise in cancer care for patients with MBC.

# 2 PREFERABLE's RESULTS

## 2.1 Exercise is (cost)-effective

The EFFECT study recruited 357 patients with MBC from centers in the Netherlands, Germany, Sweden, Spain, Poland and Australia. This randomized controlled study showed that exercise resulted in significant positive effects on both primary outcomes. Physical fatigue was significantly lower for the exercise group compared to the control group, at 6 and 9 months. Health Related Quality of Life was significantly higher in the exercise group, at 3, 6 and 9 months. Moreover, numerous other positive outcomes were observed, most notably on physical functioning, role functioning, social functioning, pain, dyspnoea and sexual health. Two serious adverse events occurred (both fractures), which were unrelated to bone metastases. Moreover, the cost-effectiveness analysis demonstrated that exercise was cost-effective from a societal perspective at the conventional level of willingness to pay of €20,000 per Quality Adjusted Life Year. In fact, the intervention resulted in cost-saving, with a reduction in costs of €163 or €1249, when supervised one-on-one or one-on-four, respectively.

## 2.2 Patients experience barriers

The PERSPECTIVE study ran alongside the EFFECT RCT and intended to generate results to support implementation of exercise as part of cancer care for people with MBC.

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To this end, PERSPECTIVE consisted of a survey including 420 MBC patients from five EU countries: Poland, Sweden, Germany, Spain, and the Netherlands; and focus groups including 44 MBC patients from four EU countries: Poland, Sweden, Germany, and Spain. Results of previous focus groups conducted in the Netherlands (doi: 10.1007/s00520-018-4619-x) are also taken into consideration here.

Key findings from PERSPECTIVE indicated that patients with MBC have an overall positive attitude towards exercise. At the same time, they experience barriers. Barriers were related to symptom load, most notably fatigue, pain and dyspnea. Additional barriers were insecurities on what to do and how to get started, accessibility and availability of dedicated exercise programs, as well as costs. Also, some patients voiced reservations towards exercise based on fear that this might increase their fatigue and pain.

## 2.3 The health care system is insufficiently supportive

In total, 22 stakeholders from 5 EU countries were interviewed, including health care insurers, policy makers (clinical directors and politicians), health care professionals (physicians, nurses), and exercise professionals (physiotherapists and exercise physiologists).

*Health care professionals*

HCPs indicated not discussing exercise with their patients as routine practice. Main barriers to recommend or enable exercise for patients with MBC were lack of knowledge about effectiveness and safety of exercise, lack of time, lack of experienced responsibility or ownership for exercise prescription, and lack of knowledge on availability of exercise programs.

*Policy makers and Health Insurers*

Health insurers considered exercise to be the responsibility of the patients, a lifestyle choice rather than health care. In line with this, they did not feel inclined to consider reimbursement. Especially, they would only reconsider reimbursement when evidence of cost-effectiveness from a societal perspective would be available. Also, health care insurers are more inclined to focus on short-term, 'hard' clinical outcomes (such as length of hospital stay, emergency room visits, etc.), whereas exercise programs usually target 'soft' outcomes (patient reported outcomes such as symptoms and quality of life).

Other policy makers (clinical directors and politicians) reported a lack of knowledge on the subject. This was, in part, due to lack of available evidence and unavailability of recommendations in clinical guidelines.

*Exercise professionals*

The main barrier experienced by exercise professionals was the limited collaboration with other healthcare professionals. Specifically, they experienced inadequate referral and handover of medical background information from the hospital, while they need this information to individualize training for patients with MBC and thereby ensure safety and effectiveness. Another issue in some of the EU countries is the small work force of qualified exercise

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professionals who can tend to the needs of patients with MBC, and the resulting lack of exercise programs.

# 3 Recommendations

The findings of the EFFECT RCT warrant implementation of exercise into routine cancer care for patients with MBC.

Based on the above main findings and the more granular results as reported in the scientific publications on the PREFERABLE project, we formulated recommendations to support this implementation. Some of these recommendations have also been published in deliverable 3.3. of this project: the final report on PERSPECTIVE. In some cases, we rephrased these recommendations based on findings from the EFFECT RCT. Additional recommendations were formulated based on the combined findings from all PREFERABLE projects.

The recommendations are aimed at different stakeholders. Recommendations could be aimed at **policy makers** (i.e., politicians, public health officials, insurers, or national health authorities), **health care managers** (i.e., hospital administrators, or clinical managers), **exercise professionals in health care** (i.e., physical therapists working in clinics and community settings, and clinical exercise physiologists), other **health care professionals** (anyone involved in the clinical care of people with MBC, including medical specialists, primary care physicians, nurses and nursing specialists, but not including the exercise professionals), and **non-governmental organizations**. For each recommendation, the relevant target group is indicated.

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## 3.1 Recommendations for policy makers

**Recommendation 3.1.1**

Policy makers should endorse and finance public health campaigns to inform MBC patients about health benefits from exercise.

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| PREFERABLE results supporting the recommendation | Patients **expect positive effects** on **physical outcomes** from physical exercise (focus groups and survey). Patients with MBC reported that maintaining or improving **endurance** and/or **muscle strength** were the main goals they would like to achieve by a supervised exercise program (survey). However, they had less knowledge about the effects of exercise on **psychological outcomes** or **fatigue,** and some feared that exercise might worsen their pain and fatigue. The **EFFECT results indicate that exercise reduces fatigue, pain, dyspnea and improves physical functioning, role and social functioning and quality of life**. Compared to exercise programs in the curative setting, it is likely that an intervention for people with MBC should last longer, at least 6 months because of the challenges involved with ongoing treatment and progressive disease. |

**Recommendation 3.1.2**

Policy makers should advocate for reimbursement by public and private health care insurers of the costs of exercise programs for MBC patients.

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| PREFERABLE results supporting the recommendation | Patients with MBC preferred supervision by an exercise professional to help them **overcome barriers.** The EFFECT RCT showed multiple health benefits of exercise for patients with MBC. **Lack of reimbursement limits accessibility to** exercise programs such as those used in EFFECT, and may thereby **result in health inequity** due to insufficient participation in exercise of patients with limited resources. The results of EFFECT show that the intervention is cost-effective from both a healthcare and societal perspective, and in fact **cost saving**. Cost-effectiveness is larger when exercise is offered group-based, and group-based exercise for this population is feasible. However, some patients may need or prefer 1 on 1 supervision, which still is cost-effective. Cost savings were observed as a result of **lower hospital costs** due to fewer emergency room visits, fewer day-care treatments; **less informal care;** and **higher productivity** due to less short-term sick leave.<br><br>In the situation that exercise is not reimbursed, results from the PERSPECTIVE survey showed that only 9% of patients would be **willing to pay** more than 50 euros per month out of pocket to participate in a |

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supervised exercise program, and for 38%, costs would be a barrier to exercising on a regular basis. Consequently, the amount that patients are willing or able to pay is in many cases lower than the costs of such a program.

## 3.2 Recommendations for health care managers

**Recommendation 3.2.1**

Healthcare manager should ensure the development of the necessary infrastructure for referral to and/or delivery of specialized exercise programming for MBC patients within the available financing.

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| PREFERABLE results supporting the recommendation | Although patients with MBC have a **positive attitude** towards exercise, many patients reported **barriers and insecurities** towards exercise, resulting from symptom load, lack of skill and knowledge and lack of accessibility of suitable exercise programs. They also indicated that an exercise professional could help them to overcome these barriers. Health care professionals said it was unclear whose responsibility exercise advice and referral is and did not feel ownership themselves. Therefore, members of the medical team caring for patients with MBC should establish clear lines of responsibility regarding **exercise counselling and referral. Country-specific conditions** and **local infrastructure** should be considered when designing and implementing exercise programs to ensure accessibility for many patients with MBC. **Active counselling** will probably lower barriers towards exercise and referral is often required to gain access to i.e., physical therapy services. |

**Recommendation 3.2.2**

Healthcare managers should ensure that there are procedures in place that periodically assess and document the specialized exercise rehabilitation needs of every MBC patient. Local policy should ensure that patients are provided with information about available exercise programs in their treatment setting and/or community.

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| PREFERABLE results supporting the recommendation | Although patients with MBC have a **positive attitude** towards exercise, many patients reported **barriers and insecurities** towards exercise, resulting from symptom load, lack of skill and knowledge and lack of accessibility of suitable exercise programs. At the same time, one of the main reasons to start or continue exercise on a regular basis would be to receive **personalized advice from a physiotherapist.** Healthcare professionals are recommended to periodically **assess** exercise levels, **advise** on the recommended level of exercise, and **refer** patients with |

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MBC who are not sufficiently active or who need supervision for other reasons to appropriate exercise programs. Embedding the steps “asses, advise, refer” in local guidelines, clinical pathways, or electronic health records will facilitate this process

## 3.3 Recommendations for clinical exercise professionals

**Recommendation 3.3.1**

A 9-month program consisting of two supervised, multimodal (balance, resistance and aerobic) exercise sessions of 1 hour per week for the first 6 months and 1 supervised and 1 unsupervised session for the last 3 months will reduce fatigue, pain, and dyspnea, and will improve quality of life in multiple domains at 6 months, and will lead to sustained effects at 9 months.
Resistance exercise intensity can be individualized using 12-repetition maximum (12-RM) muscle strength testing. For participants with bone metastases, it is recommended to not perform 12-RM testing for exercises that loaded the body regions with bone metastases, but instead start low and progress slow and avoid certain exercises. Aerobic exercise intensity can be tailored to the participants’ fitness levels using the Maximal Short Exercise Capacity (MSEC) and estimated $W_{peak}$ with the Steep Ramp Test (SRT). Interval training can be periodized using different paradigms. The intensity of both the aerobic and resistance exercises can be gradually increased during the exercise program and continuously adjusted, depending on the health status of the participant. The Borg RPE scale can be used to further fine-tune the intensity during the training session.
In addition to the supervised exercise program, participants should be encouraged to engage in 30 minutes of home based moderate aerobic exercise (i.e., brisk walking or cycling) on the other days.

PREFERABLE results supporting the recommendation

The program as described briefly above was used in the PREFERABLE EFFECT RCT, where it was shown to be effective and cost-effective. Detailed testing and training manuals can be found at the PREFERABLE website https://www.h2020preferable.eu/exercise-program/

Please note: Alternative exercise prescriptions and modalities that achieve similar exercise volumes might also be effective and could be considered to accommodate individual patients’ needs, preferences and abilities. Clinical exercise professionals should consult the medical team to retrieve medical information to tailor the exercise program to the patients’ needs and abilities. In case of medical questions or for medical assurance, the medical team should be consulted as well.

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## Recommendation 3.3.2

Clinical exercise professionals should have specialized training to acquire additional skills and knowledge to work with patients with MBC.

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| PREFERABLE results supporting the recommendation | Patients report that MBC or treatment symptoms can be barriers to exercising and their varying health condition should be taken into account for exercise prescription. All exercise professionals in the EFFECT trial were trained in supervising exercise for people with cancer. Specific training protocols were used to ensure safety for exercising with bone metastases. In the EFFECT trial 2 serious adverse events occurred, neither of these was related to bone metastases. Based on the issues voiced by patients and the high level of tailoring required to accommodate the capabilities and barriers of individual MBC patients in EFFECT, knowledge about MBC and how training should be adapted to disease and treatment-related issues should be considered a prerequisite for safe and effective supervision. |

## Recommendation 3.3.3

Clinical exercise professionals should take into account the individual health condition, abilities, needs and previous experiences with exercise of MBC patients when prescribing exercise to patients with MBC

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| PREFERABLE results supporting the recommendation | Patients prefer flexibility with regard to the intensity of the exercise program because their **physical condition varies** over the course of their treatment. In addition, patients may experience **physical limitations** (e.g., bone metastases), which require a **tailored** exercise program and **close supervision** or advice on correct execution of exercises (focus groups). Barriers to participating in exercise programs regularly mentioned by patients in the survey include pain, fear of falls or injury and being unsure how much exercise to do.<br><br>Overall, having **previous positive physical** or **emotional experiences** from exercise were reported to be the main facilitators to start or continue exercising on a regular basis. We found that patients with a **positive attitude** towards exercise and an active lifestyle before diagnosis often had a positive attitude after diagnosis. The supervision as offered in the EFFECT RCT led to a high adherence of 77% and compliance to exercise prescriptions that varied from 59% to 100% with a median of 71%.<br><br>Please note: Patients with no or limited physical activity history may have greater difficulty overcoming the perceived barriers to starting exercise and |

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may need more explanation and encouragement. Wording of information should be adjusted to individual patients' knowledge about exercise and related concepts. Motivational strategies could tap into previous positive experiences.

**Recommendation 3.3.4**

Clinical exercise professionals should help MBC patients to develop the necessary skills for self-directed exercise to maximize health-related outcomes.

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| PREFERABLE results supporting the recommendation | While increasing muscle strength was reported as one of the main goals the participants would like to achieve by exercising, only 35% of the participants indicated having the necessary skills to engage in resistance-based exercises. Also, preferred forms of exercise were not always in line with the type and intensity of exercise needed to gain health benefits according to current guidelines, or the program as proven effective in EFFECT. In the EFFECT-RCT, one out of two supervised sessions per week was substituted with one unsupervised session for the last three months. Participants developed the necessary skills to complete the unsupervised sessions during the first six month of the intervention period. In addition, they were specifically instructed by their trainer. Indeed, sustained beneficial effects of exercise were observed at 9-months, showing that participants were able to self-direct their exercise to maximize health-related outcomes.<br><br>Please note: Skills for self-directed exercise should include knowledge of which exercises are safe, proper form, how to progress or digress, and when to consult an exercise professional. |

**Recommendation 3.3.5**

Clinical exercise professionals should assess and acknowledge potential barriers (i.e., fatigue, pain, mood, or habit) to engage in exercise and provide strategies to overcome these barriers as a fundamental part of the treatment process.

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| PREFERABLE results supporting the recommendation | Patients report that MBC or treatment-related symptoms are barriers to exercising on a regular basis. These included feeling to weak (44%), tiredness (42%), fear of falls and injury (33%) and shortness of breath (26%). Some negative outcome expectations were voiced regarding the effect of exercise on fatigue and pain. The EFFECT RCT demonstrated that **exercise reduces fatigue, pain and dyspnea.** These results were even |

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more pronounced in subgroups of patients with higher levels of symptoms at baseline. Patients also mentioned safety concerns. The EFFECT RCT provided no evidence that exercise for this population is more unsafe than for a general population. In particular, no metastases-related adverse events occurred. Finally, participants believed that exercise professional could help them overcome their barriers by providing individually tailored programs and ensuring that exercises were carried out correctly.

Please note: During supervised programs, the exercise professional should provide a **safe environment**. Exercise professionals should actively ask and care about symptoms and modify exercise programs appropriately to match individual abilities. Clinical exercise professionals should be aware that the optimal exercise intensity and duration is not (immediately) achievable by all patients. Clinical exercise professionals should **consult** the medical team to retrieve medical information to tailor the exercise program to the patients' needs and abilities. In case of medical questions or for medical assurance, the medical team should be consulted as well. Clinical exercise professionals are encouraged to report on the progression of the patient to the medical care team. Clinical exercise professionals should provide the opportunity for **one-on-one** supervision to ensure appropriateness of exercises, correctness of execution and reassurance for patients with exercise-related fears. **Group training** options should be offered, either composed of people with (metastatic breast) cancer or of people with other diseases/comorbidities, dependent on the patients' preference. If **home training** is preferred, an initial instruction and guided program is advisable.

## 3.4 Recommendations for other health care providers

**Recommendation 3.4.1**

Health care providers and especially primary care providers (physicians, nurse practitioners) should **assess** 1) the current level of exercise patients with MBC and 2) the presence of barriers to exercise and 3) the need for referral to an exercise specialist. This evaluation should be repeated in subsequent visits.

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| PREFERABLE results supporting the recommendation | The self-reported exercise behavior of respondents to the survey was below the current recommendations for cancer survivors. Similarly, exercise behavior of participants in the EFFECT RCT did not meet guideline recommendations. At study start, the median minutes per week spent on strength exercise and moderate to vigorous aerobic exercise were both 0, and in the control group this did not change throughout the study.<br>Exercise recommendations from their doctor was the highest rated facilitator to exercise for patients with MBC in Poland. Patients in all |

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countries reported several barriers to engage in exercise, related to their symptoms or insecurities. The EFFECT RCT demonstrated that many symptoms that are barriers to exercise, in particular fatigue, pain and dyspnea can be reduced by exercising.

**Recommendation 3.4.2**

Health care providers should **advise** patients about health benefits of exercise and encourage them to gradually increase their exercise levels towards the recommended amount of exercise to achieve those benefits (150 min/week aerobic exercise and 2x/week strength training). They should educate MBC patients about which of their barriers would likely improve by exercising, and where possible help resolve other barriers.

PREFERABLE results supporting the recommendation

Exercise recommendations **from their doctor** was the highest rated facilitator to exercise for patients with MBC in Poland. We found that patients with a **positive attitude** towards exercise and an active lifestyle before diagnosis often had a positive attitude after diagnosis (focus groups). Half of the patients (51%) reported knowing **how much exercise** they should do to gain health benefits. However, only 6% of the survey participants were correct (140 to 160 minutes per week). Patients also reported multiple **barriers** to exercising on a regular basis (survey). Some patients expect exercise to decrease their ability to perform daily activities (3%), increase their level of fatigue (4%) or worsen their pain (5%). The EFFECT study demonstrated that the recommended levels of physical exercise are feasible and effective for reducing symptoms and improving quality of life. Other barriers, i.e., practical barriers, lack of motivation, or transportation problems cannot be reduced by exercising, but do require problem-solving strategies. In particular, considering the low willingness to pay reported in the PERSPECTIVE survey, financial barriers should be actively queried when there is no reimbursement for supervised exercise.

**Recommendation 3.4.3**

Primary health care professionals (physicians/ nurse specialists) should **refer** patients with MBC who are insufficiently active or who are not safe to exercise on their own, to a qualified trainer/ program.

PREFERABLE results supporting the recommendation

The positive effects of exercise on MBC (treatment) related symptoms and health related quality of life demonstrated by the EFFECT RCT were obtained under close supervision of qualified exercise professionals. Patients reported insufficient skills for resistance exercise. According to respondents to the PERSPECTIVE study, one of the main reasons to start or continue exercise on a regular basis would be to receive personalized

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advice from a physiotherapist. Also, many respondents to the PERSPECTIVE survey had a preference for supervised exercise and believed that this would help them overcome their exercise barriers.

**Recommendation 3.4.4**

Health care professionals should acknowledge that the needs for social interaction and peer support vary from one MBC patient to another, and take this in consideration when referring to exercise programs.

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| PREFERABLE results supporting the recommendation | Many patients preferred group training, as they enjoy contacts with other people and the opportunity to socialize during exercise (focus groups). However, some patients favored exercising individually with an exercise professional (focus group). In all countries, the first preference for exercise supervision was supervision by either a fitness instructor or a physiotherapist (survey). The first most common preference for company to exercise with differed by country. Patients from Sweden preferred to exercise alone; in Poland, patients' first preference was to exercise with the healthy individuals; in Germany, patients preferred to exercise with other patients with cancer (survey). Patients from the Netherlands and Spain most often indicated no preference (survey). |

## 3.5 Recommendations for non-governmental organisations

**Recommendation 3.5.1**

Non-governmental organizations should inform patients with MBC and other stakeholders about expected health benefits from exercise.

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| PREFERABLE results supporting the recommendation | Patients **expect positive effects** on **physical outcomes** from exercising, and reported that maintaining or improving **endurance** and/or **muscle strength** were the main goals they would like to achieve by a supervised exercise program (survey). However, they had less knowledge about the effects of exercise on **psychological outcomes** or **fatigue**. The EFFECT RCT showed that exercise for patients with MBC is beneficial on many health-related and quality of life outcomes. Policy makers and health insurers demonstrated low awareness of the benefits of exercise for patients with (M)BC. In addition, health insurers seemed to regard exercise as lifestyle rather than health care. |

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**Recommendation 3.5.2**

Patient organizations should lobby public officials in their countries to provide reimbursement for supervised programs and can consider fundraising to pay for supervised exercise programs for MBC patients.

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| PREFERABLE results supporting the recommendation | Patients with MBC preferred supervision by an exercise professional to help them **overcome barriers.** At the same time, only 9% of patients would be **willing to pay** more than 50 euros per month out of pocket to participate in a supervised exercise program, and for 38%, costs would be a barrier to exercising on a regular basis. Consequently, the amount that patients are willing or able to pay is in many cases lower than the costs of such a program. The EFFECT RCT showed multiple health benefits of exercise for patients with MBC. **Lack of reimbursement limits accessibility** exercise programs such as those used in EFFECT and may thereby **result in health inequity** due to insufficient participation in exercise of patients with limited resources. The results of EFFECT show that the intervention is cost-effective from a societal perspective, and in fact **cost saving**. |

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## Recommendation 3.5.3

Patient organizations should provide MBC patients with practical recommendations on how find a supervised exercise program and motivate them to keep up with it despite barriers.

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| PREFERABLE results supporting the recommendation | Patients with MBC reported that they were unsure how to start exercising. Also, they considered lack of appropriate places to exercise or access to exercise programming as barriers. Also, symptoms such as fatigue, pain and dyspnea were reported as barriers, while the EFFECT RCT results demonstrate that exercise reduces such symptoms. |

## Recommendation 3.5.4

Health care professionals and exercise professionals should encourage MBC patients to obtain information about the availability of reimbursement for exercise programs.

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| PREFERABLE results supporting the recommendation | 57% of the survey participants did not know whether their current health insurance company reimburses exercise or rehabilitation programs for people with cancer. This percentage was similar across different countries: Germany 58%, The Netherlands 62%, Poland 41%, Spain 54% and Sweden 69%. For 38% of the participants, costs would be a barrier standing in the way for exercising on a regular basis (ranging from a little to very much). Ultimately, the individual patient is responsible for obtaining information from their health care insurer about reimbursement of exercise programs. Improving patients' knowledge about available reimbursement may lower the cost-barrier for patients who qualify for such reimbursement, but who are currently unaware of this. |

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Recommendations presented in this document are based on a study funded by the European Commission Research & Innovation Horizon 2020 program under grant agreement No. 825677.