BMC Cancer

STUDY PROTOCOL

Open Access

# Exercise as part of survivorship care in metastatic breast cancer: protocol for the randomized EMBody trial

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## Abstract

**Background** Exercise is associated with improved survival, physical functioning, treatment tolerability, and quality of life in early-stage breast cancer. These same endpoints matter in metastatic breast cancer (MBC). Prior trials in MBC have found exercise to be not feasible or of limited benefit, possibly due to inclusion of patients with heterogeneous disease trajectories. Patients with MBC have variable disease trajectories and supportive care needs; those with indolent MBC have longer life expectancy, lower symptom burden and distinct priorities, and are well-positioned to participate in and benefit from an exercise program. The EMBody trial aims to determine the impact of a multimodal exercise intervention on cardiorespiratory fitness, physical function, body composition, and patient-reported outcomes, specifically in patients with stable, indolent MBC.

**Methods** Eligible patients have MBC with no evidence of disease progression on current therapy in the prior 12 months and cannot be receiving cytotoxic chemotherapy. The trial aims to enroll 100 patients, randomized 1:1 to the exercise intervention versus usual care, stratified by baseline function. The virtually-delivered exercise intervention arm achieves moderate intensity exercise with exercise physiologists 3 days/week for 16 weeks. The 60-minute sessions include aerobic, resistance, balance and stretching exercises. The exercise arm receives informational sessions on the role of exercise in cancer and principles of habit and self-efficacy. The primary endpoint is 16 week change in fitness on a ramp treadmill test between the exercise and control arms. Secondary endpoints include change in a physical function, muscle mass assessed by CT scans, and PROs of fatigue and quality of life. Exploratory analysis includes behavioral modifiers of exercise adherence and effectiveness and serologic measures of inflammatory, metabolic, and immune pathway biomarkers.

**Discussion** The EMBody trial evaluates exercise in a unique patient population with indolent, non-progressive MBC. Patients living with MBC experience similar symptom burden to those undergoing therapy for early-stage disease and the benefits achieved with exercise could be similarly impactful. This trial will contribute evidence to support

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expansion of exercise recommendations, among other survivorship care efforts, to those living with metastatic disease. Clinical trial information: NCT05468034.

**Trial registration** NCT05468034. Date of registration: 7/12/2022.

**Keywords** Breast cancer, Indolent metastatic breast cancer, Exercise, Supportive oncology, Cardiorespiratory fitness

## Background

Exercise is associated with improved survival, physical functioning, treatment tolerability, and quality of life in patients with early-stage breast cancer. Meta-analyses of observational studies show a 31% reduction in breast cancer mortality and a 48% reduction in all- cause mortality in patients with higher levels of physical activity after diagnosis, compared with lower levels [1]. Additionally, there is robust prospective evidence for the efficacy of exercise interventions to improve cardiorespiratory fitness (CRF) [2, 3], physical function [2, 4], and muscle mass [5] in early stage breast cancer [6]. Each of these endpoints are associated with improved survival in the curative setting [7–9].

Outcomes improved by exercise in early-stage breast cancer are also important for those living with metastatic disease. CRF is a predictor of worse cancer- specific survival in metastatic breast cancer (MBC) [10, 11]. Across the breast cancer continuum, CRF measured by $VO_{2peak}$ is significantly worse than in sedentary, age- matched controls without breast cancer, and is lowest in patients with MBC. In a prior cross sectional study [11], 44% of patients with MBC had CRF less than what is needed for functional independence. These patients had a 78% increased risk of death compared to MBC patients above that threshold ($VO_{2peak}$<15.4 ml*kg$^{-1}$*min$^{-1}$ HR 0.32, 95% CI 0.16–0.67, $p$=0.002). In addition to poor fitness, there is a high prevalence of physical impairment and poor physical function in MBC [12], with few patients receiving treatment for these as part of comprehensive supportive care [13]. Objective and subjective physical function are prognostic of increased mortality in patients with cancer, including those with metastatic disease [9, 14, 15]. Additionally, low muscle mass is associated with worse survival in advanced solid tumors [16, 17], and with worse treatment tolerability and shorter time to progression in patients with MBC [18, 19].

Despite numerous prospective trials, retrospective analyses, and observational studies evaluating the influence of exercise in the curative setting, few have evaluated the impact of exercise in patients living with MBC. Scott et al [20] randomized 65 patients with MBC to aerobic training for 12 weeks versus a stretching control. Almost one-third of patients ($n$=9/33) in the intervention arm discontinued due to disease progression, pain, or lack of motivation; thus, it was concluded that aerobic exercise is not feasible in this population. In the Metastatic Exercise Training Trial (METT), Ligibel et al. completed a randomized trial of partially supervised aerobic training for 16 weeks versus usual care among 101 patients with MBC. The exercise arm did not demonstrate statistically significant improvements in physical activity, physical functioning, or CRF. Importantly, both of these trials included patients across the broad spectrum of MBC, the majority being heavily pretreated and receiving chemotherapy. When focused only on patients receiving endocrine therapies rather than cytotoxic chemotherapy, a post- hoc exploratory analysis of the Ligibel trial demonstrated differences in CRF outcomes by treatment type (p for interaction 0.003), with women treated with endocrine therapy experiencing low drop-out rates and improvements in CRF in the exercise arm versus usual care (increase of 1.04 min versus 0.05 min on a Bruce ramp test). Trajectories of disease in MBC are very heterogeneous, from very indolent to rapidly progressive disease. The functional ability, life expectancy, and supportive care focus of MBC survivors vary substantially based on disease trajectory; therefore, broad-based inclusion into exercise trials and programs in the metastatic setting may limit the realization of benefit. There is a need for trials focused on more homogeneous populations.

Patients with MBC have lower aerobic fitness, reduced muscular strength, and less daily physical activity compared to counterparts without MBC [12]. A combination of resistance and aerobic exercise can address a spectrum of physical and cardiovascular declines from cancer and cancer-directed therapy. During the COVID-19 pandemic, virtually supervised exercise was found to have several advantages in cancer survivors including maintaining rigor of supervised exercise, improved adherence in a home-based setting, and improved freedom with location [21]. Studies have also reported preliminary efficacy of virtually supervised exercise on cardiovascular endurance and physical function [22], superiority in physical activity and reduction in sedentary behavior [23], and improved patient-reported outcomes of quality of life, feeling of support and loneliness, and anxiety/stress [22, 24, 25].

Prescribed exercise from a clinician, rather than passive recommendation, has been shown to improve the initiation and intention to exercise in patients with breast cancer [26]. However, adherence to exercise remains a challenge as patients experience unique barriers such as

excessive fatigue, treatment side effects, lack of motivation, and lack of knowledge about the impact of exercise while receiving cancer treatment [27, 28]. These challenges are magnified in the MBC population due to the complexity of individual, environmental, and cognitive barriers to exercising regularly during treatment [29, 30]. A potential solution to improve adherence is to incorporate behavior change coaching techniques grounded in health behavior theories [31]. Moreover, the application of behavior change theory allows for the identification of mechanisms of behavior change attributed to the intervention [31, 32], enhancing reproducibility for future study designs. However, there is limited available data to identify the most important behavioral determinants for exercise adoption and maintenance among patients with MBC [33]. This indicates a need to design a theory-guided exercise intervention to investigate the efficacy of exercise on the health and well-being of MBC patients while identifying the behavioral determinants influencing exercise initiation, adoption and maintenance despite the challenging barriers faced by patients.

The Integrated Behavior Model (IBM) integrates both individual-level determinants from multiple theories, such as Theory of Planned Behavior and Health Belief Model, and environmental factors, providing a robust framework for understanding and influencing exercise behavior [34]. The IBM emphasizes the sustainability of behavior incorporating environmental determinants to create supportive environments [35] that sustain behavior change over time by empowering patients to overcome barriers to exercise [36, 37]. The central construct of the IBM model is the intention to engage in exercise, which is influenced by proximal cognitive predictors of exercise behavior including attitudes, subjective norms, and self-efficacy [38]. A unique aspect of the IBM model is the emphasis on post-intention factors once the intention to exercise is established. These post-intention factors are crucial for the successful adoption of exercise and include providing a supportive environment (e.g., access, cost, clinician support) and building the necessary skill set to execute the exercise (e.g., techniques, knowledge, individualized exercise training), and habit formation [39]. The combination of these elements makes the IBM model a parsimonious, testable, practical, and integrated framework for designing interventions that are tailored, sustainable, and capable of achieving long-term health benefits for unique populations, such as MBC patients [40, 41].

Our cross-disciplinary team designed the two-arm, IBM-guided, randomized EMBody trial evaluating a 16-week multimodality, virtual 1:1 exercise intervention versus usual care delivered to women with indolent MBC. The primary objective is to evaluate the impact of exercise on CRF as estimated by minutes of exercise tolerance on the Modified Bruce treadmill protocol. Secondary objectives will evaluate the efficacy of the exercise intervention to improve physical function, quality of life, and body composition measured on computed tomography (CT) scans obtained for disease monitoring. Exploratory objectives will evaluate behavioral constructs predictive of exercise uptake and adherence in this population, and changes in serologic markers of inflammation. Long-term, this trial aims to provide evidence to support enhanced survivorship and supportive care efforts for those living with metastatic disease, and to acknowledge the differing needs of patients with different disease trajectories.

## Methods

### Study design

The EMBody study is a prospective, randomized, two-arm trial enrolling 100 participants into a virtual, supervised, progressive intensity aerobic and resistance exercise intervention versus usual care in patients with indolent MBC, defined as no progression on current therapy in the prior 12 months and not receiving cytotoxic chemotherapy. Participants are randomized 1:1 to exercise or usual care in blocks of four, stratified by frailty based on the short physical performance battery (SPPB) [42]. The primary endpoint will assess 16-week change in CRF between the exercise and usual care arms defined by minutes on a Modified Bruce treadmill protocol. Secondary endpoints include change in physical function by SPPB score, muscle mass assessed by CT scan, and patient-reported outcome measures (PROMs) of fatigue, physical functioning, and quality of life. Assessments are performed at baseline, 8 weeks, and 16 weeks, with long-term follow up occurring every 6 months thereafter (Fig. 1, schema).

### Patient recruitment

Potential participants will be identified at Schwarz Cancer Center, IU Health West, Eskenazi Marion county hospital, and the Indiana University Simon Comprehensive Cancer Center breast oncology outpatient clinics or by referrals from outside physicians. We will approach all patients with indolent MBC that has been stable for the last 12 months to avoid bias in our recruitment process. Participants who appear to be eligible for this trial based on the criteria in Table 1 will undergo the informed consent process and be screened for eligibility. Those who opt to not participate will be documented, including the reason for not participating, if known. Participants will be paid $150 in the form of a gift card at completion of the 16-week assessment in both the intervention and usual care arms to compensate for time spent on assessments.

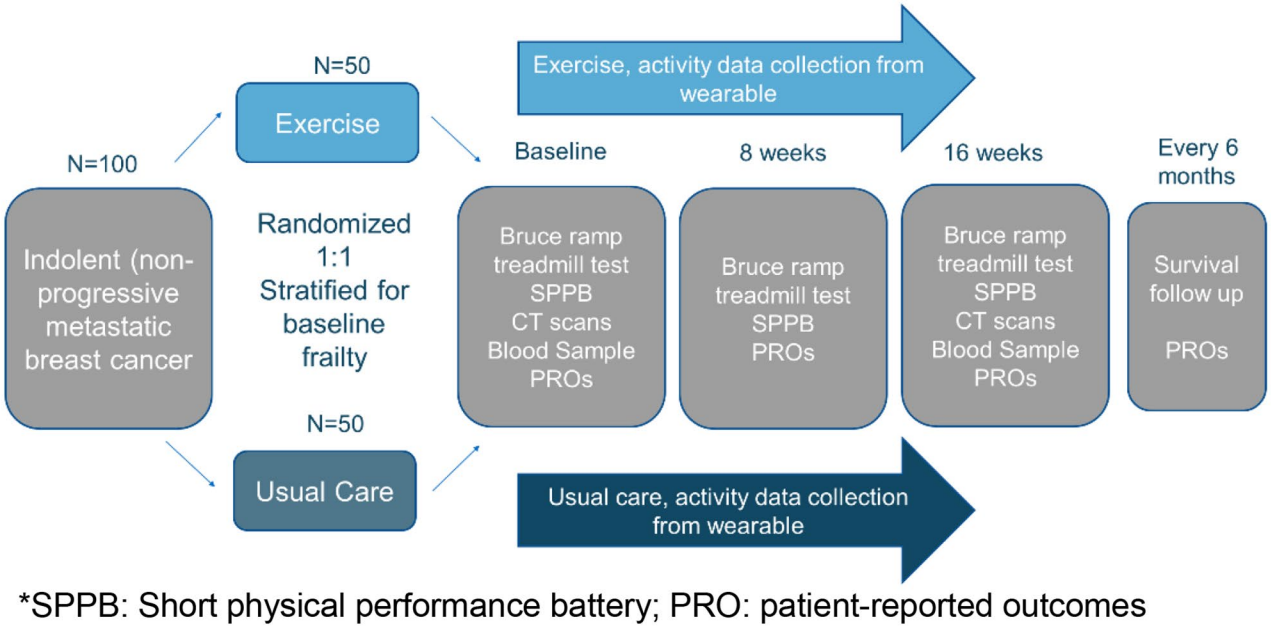


**Fig. 1** Schema

**Table 1** Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Age ≥ 18 years | Receiving cytotoxic chemotherapy |
| Stage IV breast cancer | Active, untreated brain metastases |
| No progression of disease in prior 12 months per treating physician<br>• Patients with no evidence of disease are eligible | Conditions precluding the safety of exercise, including:<br>• fragility fracture, congestive heart failure, uncontrolled angina, recent or planned orthopedic surgery, uncontrolled asthma or dyspnea required oxygen, symptomatic peripheral vascular disease, or any comorbid condition precluding exercise per the treating physician |
| ECOG performance status 0–2 | |
| Ability to march in place for 30 s without assistive device | |
| Currently not meeting physical activity guidelines (< 150 min of moderate or vigorous activity/week per the IPAQ) | |
| Cellular device compatible with iOS 15 or Android OS 7 | |

*IPAQ: International Physical Activity Questionnaire; ECOG: Eastern Cooperative Oncology Group; ADC: antibody drug conjugate

### Intervention

The intervention is behavioral theory based, multimodality exercise program designed to increase aerobic and resistance exercise with the goal of improved CRF and physical function in those living with MBC. Participants randomized to the exercise arm will work with an exercise physiologist for 60-minute sessions occurring three times weekly for 16 weeks. Schedules are determined by the participant and their trainer with oversight by the study team, ideally occurring at similar times each day, facilitating habit formation. Each training session will be delivered virtually over a HIPAA compliant Zoom platform. At their baseline visit, patients are oriented to the Zoom platform, as well as to a Garmin Vivoactive accelerometer and a Polar heart rate monitor to wear during sessions.

The virtual exercise sessions consist of (1) 30 min of cardiovascular exercise performed in Tabata style, (2) 20 min of resistance training targeting major muscle groups, and (3) 10 min of balance and stretching exercises. During sessions, patients will wear provided Polar Verity Sense heart rate monitors with a training goal of moderate to vigorous intensity, defined as 40–80% of heart rate reserve. Based on the participant's rate of perceived exertion (RPE), heart rate, and individual response during each session, trainers will follow an algorithm designed by the PI and collaborators to progress or regress intensity level based on the FITT-VP principle as recommended by the American College of Sports Medicine (ACSM) [43]. Exercise physiologists are given parameters based on average RPE and heart rate during the aerobic session for progressing participants to higher or lower levels, or to contact the study team for unexpectedly high heart rate or RPE. The starting intensity is determined by the participant's baseline physical function (example guidance in Table 2). In this way, the

**Table 2** Aerobic exercise targets based on baseline physical function

| Exercise Group | SBBP Score/Gait Speed | Target RPE | Target HRR | Work: Rest |
|---|---|---|---|---|
| Low Intensity | SPPB score ≤ 8 | 2–3 | 40–55% | 30 s:30 s |
| Moderate Intensity | SPPB > 8 and gait speed < 1.5 m/sec | 3–4 | 55–70% | 40 s:20 s |
| High Intensity | SPPB > 8, and gait speed > 1.5 m/sec | 5–7 | 70–80% | 45 s:15 s |

*SPPB: short physical performance battery, RPE: rate of perceived exertion, HRR: heart rate reserve

intervention is standardized but individualized and can be adjusted depending on the participant's medical status on a given week.

The exercise physiologists will additionally help the participant plan individual activity outside of the supervised sessions, with a total goal of 150 min per week of moderate intensity cardiovascular exercise. This is the recommended amount for cancer survivors per ACSM, endorsed by the American Society of Clinical Oncology (ASCO) [44, 45], and is associated with reduced breast cancer recurrence and death in early stage disease [1, 46].

To facilitate exercise adoption and maintenance based on the constructs of the IBM model, two educational sessions were developed, each lasting one hour and held virtually one month apart. These sessions include evidence-based content focusing on knowledge, attitude, subjective norms, self-efficacy, habit formation, and individual and environmental barriers. Each participant is given a letter of support from their treating oncologist. Exercise sessions are scheduled in advance and done at similar times each day, and self-monitoring is performed using activity logs.

### Intervention fidelity

Fidelity will be maintained using strategies consistent with NIH Behavior Change Consortium best practices [47]. Exercise physiologists who are training patients will meet structured criteria for rating skill acquisition. A standardized intervention manual will be provided. The study team will use a REDcap database to keep field notes to document delivery and details of the intervention sessions. The study team will randomly review 10% of exercise sessions, and if an exercise physiologist is not compliant with the protocol and documentation, they will be removed, replaced, and undergo remediation.

### Usual Care

Participants randomized to usual care will receive care per their treatment team. Usual care participants are encouraged to exercise but will not be provided components of the intervention. Participants will be given usual care handouts and education at baseline from ACSM [44]. After completing the 16-week visit, the study team will actively set up the participants with community resources, including the IUSCCC MOVE program, delivered as part of clinical care at IUSCCC and partnerships with other community organizations such as the YMCA.

### Outcome measures

#### *Cardiorespiratory fitness*

The primary endpoint is change in $VO_2$peak, as estimated by time on the treadmill using a Modified Bruce treadmill protocol. The test will begin at a speed of 1.7 miles per hour and no elevation. The speed or elevation, or both, will increase every 3 min until the participant has reached 85% of their maximum age predicted heart rate, maximum RPE, or has requested that the test be stopped. The Modified Bruce protocol has gained popularity in recent years because the work rate increases in a constant and continuous manner, making it ideal for patients with comorbid conditions [48–50]. Total minutes spent on the treadmill protocol, peak HR, and perceived exertion level will be recorded.

#### *Subjective physical activity*

Physical activity is not distal outcome in this study but is a proximal measure of behavior change. At the baseline visit, participants in both the exercise and usual care arms will either be provided a wearable accelerometer (Garmin VivoActive) or will provide information to access data from their current wearable of choice (Apple, FitBit, or Garmin). Given that many patients already have these, this will be easier for participants to use what they are already familiar with and enjoy wearing. Data will not actively be intervened upon during the study, but analyzed afterward. Patients will be recommended to wear their device during all waking hours aside from showering or swimming throughout the study period. Those who are not uploading wearable data from either arm will be contacted by the study team on a bi-weekly basis.

#### *Short physical performance battery*

Physical functioning will be assessed using the SPPB [51], a standardized protocol encompassing measures of gait speed, balance, and strength. Higher scores represent greater function. The SPPB contains: (1) balance test of ability to stand with feet together, feet in semi-tandem, and tandem stance, (2) gait speed test with participants walking at normal pace for 4 m and (3) chair stand test with participant rising from seated without arms 5 times.

#### *Patient-reported outcome measures*

Questionnaires will be delivered during in person visits at screening, baseline, 8 week, and 16 week visit. Self-reported physical activity will be recorded using the

International physical activity questionnaire (IPAQ) [52]. This will be used for eligibility screening and as an outcome measure of change in self-reported physical activity between the arms. The PROMIS-29 questionnaire will be used to assess change in patient-reported function and quality of life between the exercise and usual care arms, including domains for physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference [53]. The Basic Fatigue Inventory [54] will be used to assess change in self-reported fatigue. A functional limitations questionnaire will be performed, asking participants to report level of difficulty in common tasks, using questions predictive of disability [55] and cancer- related mortality [15]. Lastly, perceived behavioral control, attitudes, and intentions will be assess using validated scales from the Theory of Planned Behavior, in addition to scales measuring motivation, habit, and planning. These items are outlined in Table S1.

#### *CT scan body composition*

Low muscle mass has been associated with poorer outcome and increased toxicity in advanced cancer [17]. Low muscle attenuation, reflecting muscle "quality" and intramuscular fat infiltration, is also associated with worse survival, treatment tolerability, and reduced function. In comparison to muscle mass, muscle attenuation correlates better with muscle strength and function [56]. Evaluation of muscle attenuation and mass will be determined using baseline and follow up CT scans collected for central review. These CT scans will be those closest to the study visits that are already being obtained per standard of care for disease monitoring in order to reduce participant burden and cost. A transverse cut at the L3 level will be extracted, as muscle area at this level is linearly related to whole body muscle mass [57]. SliceOmatic software (version 5, Tomovision) will be used to process images, providing a highly accurate estimation of cross- sectional skeletal muscle area and muscle attenuation with high inter-observer reliability [58]. The software is semi-automated and will be run by two independent investigators, with a subset of images read by both investigators to determine a coefficient of variation. Muscle mass is defined as skeletal muscle index (SMI, lean muscle area/height, $cm^2/m^2$) and muscle attenuation is measured in Hounsfield units (HU).

#### *Biochemistry*

Plasma and serum samples will be collected for later exploratory analysis of biomarkers of response to exercise such as inflammatory markers and metabolomics.

### Sample size

An increase of 1.0 MET (metabolic equivalent task) in exercise capacity is associated with improved survival in cancer patients and in the general population, and is a clinically meaningful change [11, 59]. An increase in 1.0 min on the Modified Bruce treadmill protocol correlates with an increase in over 1.0 MET. Using Wilcoxon rank sum test with two-sided alpha of 0.1, to have 81% power to detect a 1.0 min difference between the exercise and usual care arms, we would need 43 patients per arm (86 total), assuming variability of 1.8 min based on preliminary data [60]. Assuming 15% attrition between baseline and 16 weeks, a total of 100 participants will be recruited (50 in each arm).

### Statistical data analysis

Data will be kept in OnCore with double data entry and data checks. Wilcoxon rank sum test will be performed to investigate the impact of exercise in women living with MBC. We will compare the intervention and usual care arms with respect to minutes spent on the treadmill protocol as the primary endpoint, as well as change in minutes spent in moderate to vigorous physical activity, physical function scores, and muscle mass and density. $P$-value $< 0.1$ will be considered significant. We will perform additional sensitivity analyses including change score analysis, linear regression, and analysis of covariance (ANCOVA).

### Safety

The Data Safety Monitoring Committee (DSMC) of the Indiana University Simon Comprehensive Cancer Center (IUSCCC) is responsible for patient safety and privacy protection, compliance with required reporting, and study integrity. The DSMC will review data compliance and patient safety on a quarterly basis. Adverse events related to study procedures will be collected on a rolling basis, with serious adverse events reported within 1 day.

### Dissemination

Study results will be presented at medical and scientific conferences as well as published in peer-reviewed clinical journals. The study collaborators include patient advocates from Pink-4-Ever Ending Disparities, Metavivor, and Project LIFE MBC, who will assist with communicating results to the community on conclusion of the study.

## Discussion

The EMBODY trial aims to evaluate the potential impact of exercise in people living with MBC. The study focuses on a novel population with indolent, non-progressive MBC and delivers an exercise intervention grounded in behavioral theory that is delivered via telemedicine. This approach was developed not only by a trans-disciplinary

team of oncologists, physical therapists, exercise physiologists, and behavioral scientists, but in collaboration with patient advocates and with community partners. Findings and experience from this trial will be scalable and generalizable to other populations and other centers. Thus far, the study has enrolled 44 of 100 planned participants with high adherence to the exercise sessions at over 80%. The study is limited to patients who agree to participate, which may present some selection bias. Therefore, the team is collecting additional information on those participants who are eligible but opt not to participate in order to design future interventions to meet those patients where they are.

Currently, over 160,000 women and men are living with MBC in the United States, a number that is expected to continue to grow. While the disease remains incurable and far from chronic, the 5-year survival rate now exceeds 30% [61]. This trial builds on previous work evaluating exercise in MBC with broad-based inclusion, which may have underestimated the potential benefits of exercise due to inclusion of participants with more biologically aggressive disease. The heterogeneous disease trajectories of MBC must be acknowledged. The EMBODY trial is the first to evaluate exercise specifically in patients with indolent, non-progressive MBC, who may have a longer life expectancy and benefit similarly from exercise as those with early-stage disease.

The American Society of Clinical Oncology (ASCO) recently published a guideline recommending that exercise be part of cancer therapy with curative intent in order to mitigate the impact of treatment; this guideline did not include patients treated with palliative intent [62]. However, patients living with MBC experience a similar symptom burden to those undergoing therapy for early-stage disease. Improvements achieved with exercise in cardiorespiratory fitness, muscle strength, physical function, and quality of life could be similarly impactful for MBC as they are in the curative setting. Evidence is needed to support expansion of exercise recommendations, among other survivorship care efforts, to those living with metastatic disease. Findings from this trial will contribute to broadening the supportive care agenda to include MBC.

**Abbreviations**

| | |
|---|---|
| MBC | Metastatic breast cancer |
| CRF | Cardiorespiratory fitness |
| IBM | Integrated Behavior Model |
| CT | Computed tomography |
| SPPB | Short physical performance battery |
| PROMs | Patient-reported outcome measures |
| PRO | Patient-reported outcomes |
| IPAQ | International Physical Activity Questionnaire |
| ECOG | Eastern Cooperative Oncology Group |
| ADC | Antibody drug conjugate |
| RPE | Rate of perceived exertion |
| ACSM | American College of Sports Medicine |
| HRR | Heart rate reserve |
| MET | Metabolic equivalent task |
| ANCOVA | Analysis of covariance |
| ASCO | American Society of Clinical Oncology |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12883-6.

Supplementary Material 1

**Acknowledgements**
The authors are grateful to the Clinical Trials Office at the Indiana University Simon Comprehensive Cancer Center and the IUSCCC MOVE cancer exercise program for assistance in the conduct of this trial.

**Author contributions**
TJB conceived the work and secured funding with mentorship from JL. MC, DN, and TJB drafted the article. All authors revised the manuscript and approved the final version.

**Funding**
This trial receives peer reviewed funding from a Susan G. Komen Career Catalyst Research (CCR) Award to T. Ballinger – grant ID 22900195.

**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval**
This study was approved by the Indiana University Institutional Review Board. All patients provided informed consent to participate.

**Conflict of interest**
The authors declare on competing interests.

**Consent for publication**
Not applicable.

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Received: 3 July 2024 / Accepted: 30 August 2024
Published online: 12 September 2024

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