Title

Exercise for Health: a randomized, controlled trial evaluating impact of a pragmatic, translational exercise intervention on quality of life, function and treatment-related side effects following breast cancer

Running head

Exercise for Health trial for women with breast cancer

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Abstract

Purpose: Exercise for Health was a randomized, controlled trial designed to evaluate two modes of delivering (face-to-face [*FtF*] and over-the-telephone [*Tel*]) an 8-month translational exercise intervention, commencing 6-weeks post-breast cancer surgery (PS). ***Methods:*** Outcomes included quality of life (QoL), function (fitness and upper-body) and treatment-related side effects (fatigue, lymphoedema, body mass index, menopausal symptoms, anxiety, depression and pain). Generalised estimating equation modelling determined time (baseline [5-weeks PS], mid-intervention [6-months PS], post-intervention [12-months PS]), group (*FtF, Tel,* Usual Care [*UC*]) and time-by-group effects. 194 women representative of the breast cancer population were randomised to the *FtF* (n=67), *Tel* (n=67) and *UC* (n=60) groups. ***Results:*** There were significant ($p<0.05$) interaction effects on QoL, fitness and fatigue, with differences being observed between the treatment groups and the *UC* group. Trends observed for the treatment groups were similar. The treatment groups reported improved QoL, fitness and fatigue over time and changes observed between baseline and post-intervention were clinically relevant. In contrast, the *UC* group experienced no change, or worsening QoL, fitness and fatigue, mid-intervention. Although improvements in the *UC* group occurred by 12-months post-surgery, the change did not meet the clinically relevant threshold. There were no differences in other treatment-related side-effects between groups. ***Conclusion:*** This translational intervention trial, delivered either face-to-face or over-the-telephone, supports exercise as a form of adjuvant breast cancer therapy that can prevent declines in fitness and function during treatment and optimise recovery post-treatment.

Keywords: Breast Cancer, Randomized Controlled Trial, Exercise, Quality of Life, Function

Introduction

With over one million women worldwide diagnosed with breast cancer each year, and improving survival rates,[1] there is an imperative for increased attention to breast cancer survivorship. Receiving treatment for breast cancer has long been associated with an array of physical and psychosocial consequences, with the type, prevalence and severity of concerns evolving with changes in the way breast cancer is treated.[2] Current estimates indicate that at 6-months post-diagnosis, 90% of women report at least one adverse treatment effect and 60% report multiple sequelae, which influence function, the ability to adhere to adjuvant breast cancer treatment, quality of life (QoL) and potentially survival.[3] Notably, even 6-years out from breast cancer, 30% of women report multiple, significant treatment-related sequelae that continue to influence longer-term morbidity and mortality.[3] Thus, there is a clear need for identifying strategies that can be integrated among current breast cancer care to optimize quality and quantity of survival.

There exists a growing and compelling body of evidence supporting the benefits of exercise following the diagnosis of cancer, in particular breast cancer, with results summarized in meta-analyses and systematic reviews.[4-6] Exercise interventions implemented during and/or following treatment lead to improvements in cardiorespiratory fitness, body composition (i.e., muscle mass and bone health), immune function, strength and flexibility, body image, self-esteem and mood, and allow for better adjustment to illness. Exercise interventions have also been shown to reduce stress, depression, anxiety and the number and severity of side effects, including nausea, fatigue and pain. These benefits have been observed in exercise interventions involving aerobic- and/or resistance-based exercise undertaken for 90+ minutes per week.[6] Further, evidence from large cohort studies indicate

that exercise may also improve survival,[7] with results supporting a dose-response relationship whereby more exercise is better than less, but possibly only up to levels which meet national physical activity recommendations (150 minutes of moderate-intensity activity per week).

To date, the majority of exercise intervention trials among women with breast cancer have evaluated supervised and clinic-based interventions, with eligibility criteria that restricts participation to those with early stage disease and no additional co-morbidities or complications that may interfere with participating in an exercise intervention.[4] While a limited number of trials have evaluated non-face-to-face intervention delivery methods,[8-16] effect of the exercise intervention on QoL, function and treatment-related side effects varies and none of these trials have compared the effect of different modes of delivery of the same exercise intervention. Thus, the current evidence base in support of exercise post-breast cancer largely pertains to the 'healthier' woman with breast cancer, who is able and willing to attend clinic-based exercise treatment.

The call to include exercise as part of the standard of care provided to women following breast cancer is getting louder.[17] However, to change clinical practice, there is a clear need for comparative effectiveness trials demonstrating feasibility and effect of exercise associated with alternative delivery modalities. It is also necessary for benefits to be observed on a heterogeneous population of women with breast cancer, such that the intervention is suitable for all women, irrespective of health and disease status and participation needs to be feasible irrespective of place of residence. Exercise for Health (EfH) was a pragmatic trial designed to evaluate the feasibility and effect of an exercise intervention delivered either face-to-face or

over-the-telephone, that if successful, could be integrated within clinical practice. The 8-month intervention delivered via both modalities was designed to assist women during active treatment periods (up to 6 months post-diagnosis), to more quickly and fully recover following treatment, and to develop the skills and confidence to become and stay physically active for the longer term. The purpose of this paper is to compare the effectiveness of the face-to-face and telephone-delivered exercise intervention on QoL, and patient-reported and clinically-measured function and treatment-related side effects.

Methods

The EfH trial (ACT RN: 012606000233527) was reviewed and approved by the Institutional Review Board (i.e., Ethics Committee) at the Queensland University of Technology and at each of the four participating hospitals. The analyses presented in this manuscript adhere to those outlined in the original grant application and presented in the baseline manuscript.[18]

Patients

A total of 194 women with a first diagnosis of invasive breast cancer were recruited into the 'Exercise for Health' trial through four participating Brisbane (Australia) hospitals between October 2006 and June 2008. Breast cancer nurses introduced patients to the trial after their initial surgery. Interested patients were then contacted by research staff three to four weeks post-surgery to discuss the trial in detail and confirm informed consent. Women aged 20 to 69 years, and residing within a 30 kilometre radius of the Brisbane central business district (to enable participation in face-to-face sessions) were eligible to participate. Exclusions were made for women who were pregnant or lactating, had plans for breast reconstructive surgery during the study period or with poor English.

Study design

While a detailed explanation of trial methods and baseline participant characteristics have been published elsewhere,[18] key features of study design are summarised below.

Timing of assessments and randomisation

Disease and treatment characteristics were extracted from the Queensland Cancer Registry, including type of cancer, type of surgery, tumour size, cancer stage, lymph node status, while a self-reported questionnaire and battery of physical tests were implemented by Exercise Physiologists blinded to group allocation at pre-intervention/baseline (5.7 weeks post-surgery, 95% CI: 5.2, 6.1 weeks); mid-intervention/6-months (25.6 weeks; 95% CI: 25.1, 26.2 weeks) post-surgery and 8-weeks post-intervention /12 months (51.4 weeks; 95% CI: 51.0, 51.9 weeks) post-surgery (Figure 1). The mid-intervention assessment coincides with mid to end of adjuvant treatment period and enables measurement of intervention effect on treatment-related symptoms at a time when they are expected to be at their highest. The final data collection time point (approximately 2 months post-intervention) allows measurement of longer-term effect on outcomes and coincides with 12 months post-surgery, which is the time point when many of the outcomes have been previously shown to stabilise.[19-21]

After baseline assessment, women were individually randomised into one of the three groups via a computer-generated, unblocked sequence of random numbers. Sixty-seven women were each randomised into the face-to-face-delivered exercise intervention group (*FtF*) and the telephone-delivered exercise intervention group (*Tel*), while sixty women were randomised

into the usual-care group (*UC*). Figure 2 details the recruitment, randomisation and follow-up process.

Intervention

For those in the *FtF* and *Tel* groups, the 8-month exercise intervention began in the week following baseline assessment (6 weeks post-surgery) (Figure 1). Key features of the intervention are presented in Table 1. The intervention involved 16 scheduled sessions (in person or via telephone) with a designated Exercise Physiologist, starting weekly and tapering to monthly contacts after 4 months. Exercise prescription was Exercise Physiologist-driven during the first third to half of the program and became more patient-driven over-time. This approach allowed patients to have their exercise prescription clinically-led during their active treatment period, when treatment-related symptoms were likely to be presenting and/or fluctuating and exercise confidence, skills and knowledge was at their lowest. The approach also acknowledges the need for longer-term behaviour change (beyond the treatment period), which would only occur if patients developed skills, knowledge and confidence to become and stay independent exercisers. At all stages of the intervention, women were progressing towards (or maintaining) the overall goal of exercising at least 4 days per week for 45 minutes (accumulating 180+ minutes of exercise per week) and incorporating both aerobic and strength-based exercises (on at least 2 days per week). Exercise starting parameters and rate of progression was individually-tailored, taking into account existing level of fitness, presence of treatment-related side effects and exercise preferences.

Usual care

Women in the UC group were given no advice outside of that provided through usual care. This varied depending on treating clinician and/or hospital and may have included receipt of verbal or written encouragement for participating in physical activity during and beyond breast cancer, but with no formal or regular advice about what to do and how to do it.

Outcomes of interest

Primary outcome: Quality of Life

The primary outcome measure was QoL, as measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B+4) questionnaire. This scale has been used widely in cancer research with high reliability and validity.[22, 23] The FACTB+4 includes 40 items rated on a five-point Likert scale ranging from 0 ‘not at all’ to 4 ‘very much’. This questionnaire includes the FACT-General (FACT-G),[24] consisting of four domains (physical, social, emotional, and functional well-being) and a breast cancer-specific subscale (FACT-B)[22] with an additional four questions specific to arm morbidity.[23] Scores were calculated according to the FACT manual,[25] resulting in total scores of 0-160, with higher scores representing better well-being. *A priori* sample size calculations indicated a minimum of 40 women per group was required to detect a clinically important difference of 8 units in overall QoL between groups or change over time (standard deviation of change in FACT-B+4 over 12 months = 10 units),[22] with 90% power and 5% type I error (two tailed).

Secondary Outcomes: patient-reported function and treatment-related symptoms

Upper-body function and treatment-related symptoms including fatigue, menopausal symptoms (including psychological, anxiety, depression, somatic and vasomotor scales) and neuropathic pain were measured by the Disabilities of the Arm, Shoulder and Hand

Questionnaire (scale: 0-100, higher score denotes worse function),[26] the Functional Assessment of Chronic Illness Therapy – Fatigue Subscale (scale: 0-52, higher score denotes lower fatigue),[27] the Greene Climacteric Scale (scale 0-63, higher score denotes higher symptom presence)[28] and the Neuropathic Pain Scale (scale 0-100, higher score denotes higher pain,[29] respectively. The Greene Climacteric Scale was also used to evaluate anxiety and depression, with women reporting scores of >10 for scale items 1-6 and 7-11 (assessed separately) being classified as clinically anxious and clinically depressed, respectively. Participants were also asked whether they had received a clinical diagnosis of lymphoedema, and if so, by whom and when.

Secondary Outcomes: clinically measured function and treatment-related symptoms

The 3-minute step test was used as a measure of aerobic fitness.[30] The step height was modified from 12 inches to 6 inches to accommodate knee and hip limitations of some of the participants (within-patient step height was standardised across all assessments). The metronome was set at 96 beats per minute and heart rate on test completion was used as the outcome measure. Lower heart rate indicates higher fitness. Upper-body strength and endurance was measured by an incremental exercise protocol combining a traditional upright row and shoulder press exercise using hand weights. Each stage lasted 20 seconds in duration and progression was made through number of repetitions and weight held. The prerequisite for advancement to the next stage was defined by maintaining correct form, range of motion and speed (as determined by the Exercise Physiologist). Stages ranged from 1 (no weight) through to 24 (3.5kg). The amount of weight held incremented by 0.5 kilograms after three completed stages, with 10 repetitions performed for each stage. The last successfully completed stage for each arm was recorded. This protocol has been successfully used in our

prior work.[31] Lymphedema status was assessed using bioimpedance spectrophy (BIS), which is a previously well described objective method of subclinical and/or pitting lymphoedema.[32, 33] In brief, BIS measurements on each arm were carried out using an Imp SFB7 monitor (Impedimed, Brisbane, Australia). The impedance of the extracellular fluid for each limb was calculated using the manufacturer's software. The ratio of impedance values, comparing the treated and untreated sides, was then calculated and converted into a lymphedema index (L-Dex) score. A participant was classified as having lymphedema when the L-Dex score was 10 or greater. Height was assessed at pre-intervention with the participant barefoot and measured to the nearest 0.5 centimetres at baseline. Body weight (kg) was measured at all three assessments using analogue Seca^{TM} scales. Weight was recorded to the nearest 0.5 kg. Weight and height were used to calculate body mass index (BMI) using the metric formula weight (kg) / height^2 (m^2) to produce a unit of measurement of kg·m^{-2}. The Active Australia Survey was used to collect information on total minutes of walking and moderate and vigorous physical activity mid- and post-intervention.[34]

Clinically relevant changes in outcomes

Clinically relevant changes in outcome were determined *a priori*, with cut-offs identified previously by us or others. Specifically, a change of $\geq$8 quality of life units,[22] $\geq$5 fatigue units,[27] $\geq$1.5 stages for clinically measured upper-body function[31] and $\geq$1 BMI unit (approximately 2.5kg change in body weight)[35] is clinically relevant with respect to perceived quality of life, fatigue, upper-body function and longer term health outcomes, respectively. Of note, these magnitudes of changes are equivalent to $\geq$½ standard deviation (sd) of baseline scores. As such, in the absence of previous work to guide clinically relevant cut-offs for our other outcomes of interest, a change of $\geq$½ sd of baseline scores was *a priori*

deemed clinically relevant and was equivalent to a change of ≥8 beats/minute for fitness (heart rate) and ≥7.5, ≥7.5 and ≥9 units for upper-body function (self-report), menopausal symptoms and pain scores, respectively.

Statistical Analysis

Summary descriptive statistics for baseline characteristics included counts and percentages for categorical variables or means (standard deviations), alternatively medians (ranges), for continuously-scaled variables. Continuous outcomes were modelled using generalised estimating equations (GEE) to determine time (baseline, mid- and post-intervention) and intervention group (*FtF, Tel, UC*) effects and the interaction between time and group. Means and 95% confidence intervals (CI) are reported for each estimate. GEEs were considered the most appropriate multivariate modelling technique, as unlike conventional repeated measures approaches, it is able to incorporate baseline data as well as all available data including those from participants with missing data over time. Intention-to-treat principles were applied to the analysis of data. No imputation was generated. All analysis was undertaken using SPSS version 18 software (SPSS inc, Chicago, IL).

Results

Flow of participants through the trial has been reported in detail elsewhere[18] and is summarised in Figure 2. Briefly, of the 402 women who were approached about the trial, 318 were deemed eligible and 194 women (61%) gave informed consent, completed the baseline assessment and were randomly allocated into one of the three trial groups (*FtF* n=67, *Tel* n=67, *UC* n=60). Reasons given for non-participation included had too many other commitments/were too busy, felt the program was not needed or were not coping. Trial

participants were on average younger, but had similar disease characteristics to the Queensland breast cancer population (data not shown). The trial retention rate was 94% at 6 months and 93% at 12 months. Women who withdrew (n=14) were similar in age, socioeconomic status and had similar disease characteristics compared to women who completed the trial and withdrawal rate did not differ by group allocation (6, 4, and 4 in the *FtF*, *Tel* and *UC* groups, respectively).

Participant characteristics

Median age of trial participants was 52 years (age range: 29-70 years). Personal and diagnostic characteristics, including body mass index, lymph node status, stage of disease and receipt of adjuvant therapy were similar for participants in the *FtF*, *Tel* and *UC* groups (Table 2). Women in the *Tel* group were more likely to be treated at a private hospital when compared with those in the *UC* group (61% and 50%, respectively) and less likely to have a mastectomy than the *FtF* and *UC* groups (22%, 39% and 43%, respectively). During the trial 69% of women underwent chemotherapy, 71% underwent radiotherapy and 64% began hormone therapy. Type of adjuvant therapy was balanced between all three groups.

Exercise trial adherence

Information about adherence in the Exercise for Health trial has been previously reported.[18] On average, the *FtF* group participated in 88% (14 of 16) of their scheduled sessions with their Exercise Physiologist. Those in the *Tel* group participated in 81% (13 of 16) of scheduled telephone calls.

Quality of life

The interaction effect between time and group was statistically significant (p=0.03) for QoL. The *FtF* and *Tel* exercise groups both reported increased QoL scores over time and by 12 months post-treatment showed clinically higher QoL (>8 FACTB+4 units) compared with baseline scores (Table 2). In contrast, the *UC* group showed a delayed QoL recovery (no change between baseline and mid-intervention) and level of improvements observed by post-intervention failed to meet the clinically relevant threshold. While the differences in change in QoL between baseline and mid-intervention, and baseline and post-intervention were similar for the *FtF* and *Tel* groups, only change in QoL for the *Tel* group differed significantly (p<0.05) compared with the *UC* groups (Table 3).

Function, treatment-related side effects and physical activity levels

Change in function (specifically, aerobic fitness) and fatigue between groups and over time differed (p<0.05). The *FtF* and *Tel* groups reported improvements in fitness over-time, which were clinically relevant by post-intervention (≥8 beats/minute heart rate declines) (Table 3). In contrast, the *UC* group reported worsening fitness at mid- and post-intervention and the differences between treatment groups and the *UC* in change in resting heart rate at mid- and post-intervention were significant (p<0.05). Fatigue improved over-time for the treatment groups, with change between baseline and post-intervention fatigue scores being clinically relevant for the *Tel* group (Table 3). In contrast, the *UC* group showed worsening fatigue between baseline and mid-intervention and improved fatigue between baseline and post-intervention, although magnitude of change was neither statistically nor clinically relevant.

Upper-body function and treatment-related side effects such as menopausal symptoms (including anxiety and depression) and pain improved over time (p<0.05) for all groups, and

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participating within the intervention did not influence the magnitude or rate of this change (Table 4). There was no difference between the mean body mass index and L-Dex measured at baseline, mid- and post-intervention for all groups (baseline BMI and L-Dex was 26.6±5.2 and 1.1±6.8, respectively). There were no statistical or clinically relevant differences between groups over time for the proportion of women with lymphoedema, clinical anxiety, clinical depression or having had experienced BMI gains of ≥1 unit (Table 5).

Of those in the *FtF* and *Tel* groups, 25% did not meet the intervention goal at mid- or post-intervention and did not increase their total physical activity by 30+ minutes (*a priori* deemed clinically relevant) between baseline and mid- or post-intervention. There were also 66% of women in the *UC* group who participated in 180+ minutes of total weekly physical activity at 6- or 12-months post-surgery and/or increased their level of activity by 30+ minutes following baseline assessment. At 12-months post-surgery, median minutes of total physical activity and walking for exercise per week was 180 (0, 840), 120 (0, 1110) and 120 (0, 1120) and 90 (0, 480), 60 (0, 360) and 10 (0, 420) for those in the *FtF*, *Tel* and *UC* group, respectively.

Discussion

Exercise, when delivered using a pragmatic, translational approach and included as part of standard care provided to women with breast cancer, leads to significant benefits with respect to QoL, function and treatment-related side effects. Specifically, gains in QoL and fitness and declines in fatigue were observed for those in the exercise groups during and following breast cancer treatment and the benefits are similar irrespective of whether the exercise is delivered face-to-face or over-the-telephone. In contrast, during the treatment period (between 6-weeks and 6-months post-surgery) those in the *UC* group experienced declines in fitness and no

change in QoL and fatigue. Beyond the treatment period, although improvements in QoL, fatigue and fitness were observed, unlike the intervention groups the change for the *UC* group was of insufficient magnitude to be clinically relevant.

An important and novel aspect of the EfH trial was the evaluation of two intervention delivery modes – face-to-face or telephone-delivered. The face-to-face delivery mode reflects the traditional approach used by Exercise Physiologists in the prescription of exercise, and at least in Australia there already exists public and private health reimbursement for use of such allied health services via this mode. While the telephone-delivery of exercise prescription does not reflect standard practice, Cancer Councils throughout Australia commonly deliver support on a range of healthy behaviours via their telephone help-line, highlighting that the necessary infrastructure to deliver exercise prescription via this mode already exists. Also, delivering an exercise intervention using the telephone has the advantage of reaching all women, irrespective of place of residence, and thus can accommodate the 30% of Australian women with breast cancer who live in rural, regional areas[36] and/or areas with limited access to specialist services. Further, the telephone-delivery of specialist services such as exercise has possible cost advantages compared to face-to-face delivery. Therefore, the evaluation of these two modes were purposely chosen as they reflect feasible delivery modes that could be integrated among standard practice quickly should the intervention prove effective. While future analysis will specifically evaluate the cost-effectiveness of EfH delivered via the telephone or face-to-face, findings presented here highlight the similarities in effect size of the exercise intervention between the two modes of delivery.

One of the many benefits associated with exercise following breast cancer is its potential to prevent treatment-related side effects particularly those associated with adjuvant therapy.[4] Participation in the EfH intervention prevented fatigue and declines in fitness, but did not seem to affect rates of lymphoedema, anxiety, depression or adverse changes in body mass index. There were also no differences observed in upper-body function, menopausal symptoms and pain between the groups. An active *UC* group (two-thirds were participating in 180+ minutes of activity per week and/or increased activity levels by 30+ minutes between baseline and mid- or post-intervention) may have precluded differences being observed between groups for these specific outcomes. Alternatively, a higher exercise dose (25% of the exercise groups did not meet the intervention goal and did not increase their total physical activity levels by 30+ minutes between baseline and mid- or post-intervention) or different delivery setting (e.g., in a supervised, clinic-based setting) may be required to illicit prevention of these specific side effects. For prevention of gains in body mass index, exercise alone may not be sufficient and may require dietary changes as well. Alternatively, it is plausible that the outcome measures lack sensitivity to detect exercise-induced changes. Nonetheless, EfH has clearly demonstrated women can feasibly participate in an exercise intervention delivered face-to-face or over-the-telephone, commencing 6-weeks post-surgery, and can do so safely, without exacerbating or initiating common treatment-related side effects. The intervention evaluated here included more frequent contact with women during the early phases of the program (weekly for 2 months and then fortnightly for 2 months) and tapering to monthly contact during the second half of the program. In an attempt to ensure optimal prevention of treatment-related side effects, future research may consider the evaluation of an intervention that tapers frequency of contact but also transitions from face-to-face contact through to telephone-contact over the intervention period. This may also

involve having a more flexible protocol with regard to contact between the Exercise Physiologist and patient, whereby when certain situations arise (e.g., no previous exercise history prior to participating in the intervention; change in treatment-related symptoms) contact increases to two-three times per week and tapers back when the participant's exercise self-efficacy has improved.

The strengths of this work relate to the recruitment of a sample generally representative of the wider breast cancer population, the evaluation of an exercise intervention that was delivered using a pragmatic approach to delivery suitable for translation into practice, assessors blinded to group allocation and application of intention to treat principles to analysis. However, there was a slight imbalance in numbers, place of treatment (public versus private hospital) and rates of mastectomy between groups following randomisation. While block randomisation may have led to better balance between groups, findings from adjusted analyses, which take into account rates of mastectomy and place of treatment, were no different to those presented within the manuscript. It is plausible that the EfH sample was more active at baseline compared with the wider breast cancer population, as is the case for the majority of exercise intervention trials following cancer.[17] While we are unable to confirm this using data, it is important to note that the impact of such a bias on trial findings would be in the conservative direction, making it more difficult to establish a time and/or group effect. Consequently, demonstrating an intervention effect on QoL, function and fatigue using a translational intervention approach, is particularly compelling.

In summary, findings from this study highlight that a translational exercise intervention implemented within 6-weeks post-breast cancer surgery is safe and effective at preventing

fatigue and declines in fitness and optimising QoL, while our previous published findings highlight that the participation in the intervention is feasible[18]. Women were interested and able to integrate an additional form of adjuvant treatment into their standard breast cancer care, with exercise being particularly appealing since it is a form of treatment that they can control and that is associated with recovery benefits, including the potential to minimise adverse effects from their other forms of breast cancer treatment. Further, demonstrating that delivery of the intervention face-to-face or over-the-telephone has similar effect is a particularly novel and exciting finding with significant implications for the integration of exercise into the standard of breast cancer care provided to all women, irrespective of place of residence and access to specialist care.

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Conflict of interest The authors declare that they have no conflict of interest.

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Figure 1. Timeline indicating timing of assessments, randomisation and intervention

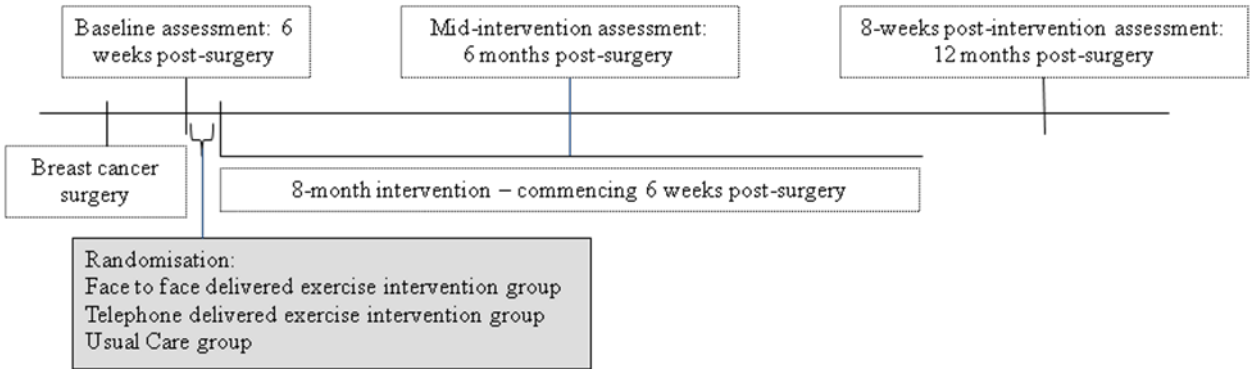

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Figure 2. Flow chart of participant recruitment and retention

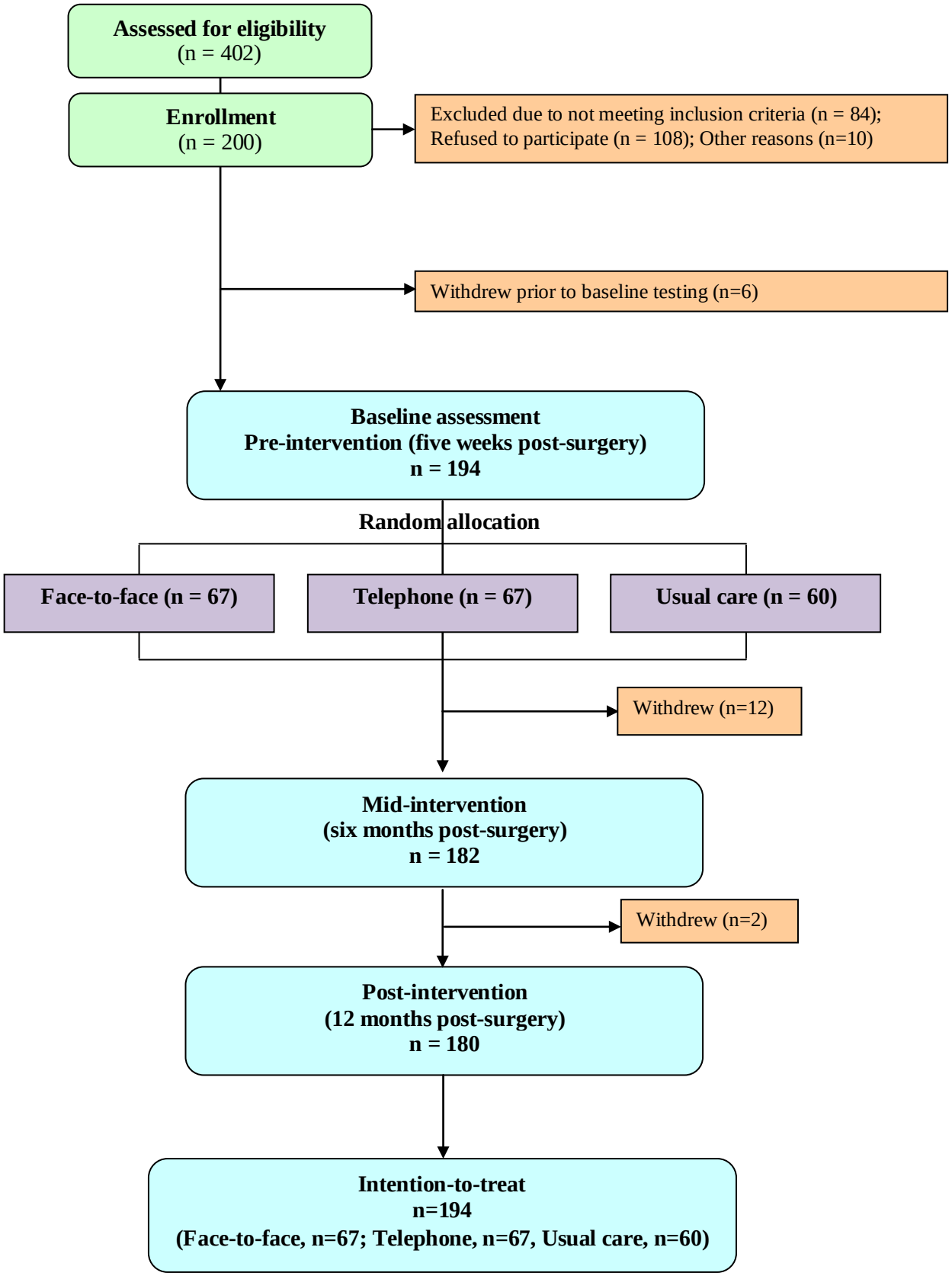

Table 1. Details of the 8-month exercise intervention

Intervention Goal	accumulating 180+ minutes of exercise per week, incorporating both aerobic and strength-based exercises				
Frequency	4+ times per week All sessions included upper and lower-body range of motion exercises as part of warm-up and cool-down				
8-month intervention	Type	Intensity	Duration/ session	Frequency of sessions with Exercise Physiologist	Responsibility of setting exercise prescription
Weeks 1-4/month 1	Aerobic	Low to moderate	20-30 minutes	Once/week	Exercise Physiologist
Weeks 5-8/month 2	Aerobic with strength introduced	Moderate	30-40 minutes	Once/week	Exercise Physiologist
Weeks 9-16/month 3-4	Aerobic and strength	Moderate to high	45+ minutes	Once/fortnight	Shared between Exercise Physiologist and participant
Weeks 17+/months 5-8	Aerobic and strength	Moderate to high	45+ minutes	Once/month	Participant
Progression and overload	Manner (that is, modification of type, intensity, duration and responsibility of setting exercise prescription) and rate was individually-tailored with exercise history, exercise confidence, adherence to prescription for previous period and presence and severity of treatment-related side effects reflecting factors that influenced progression and overload.				

Table 2. Baseline characteristics of study participants by group allocation (n=194)

	Face-to-face group n=67	**Telephone group n=67**	**Usual-care group n=60**
Age (years)			
mean (SD)	51.2 (8.8)	52.2 (8.6)	53.9 (7.7)
Body mass index (kg/m^2)	**n (%)**	**n (%)**	**n (%)**
Underweight (<18.5)	1 (1.5)	1 (1.5)	3 (5.0)
Healthy (18.5-24.9)	31 (46.3)	28 (41.8)	23 (38.3)
Overweight (25-29.9)	22 (32.8)	19 (28.4)	22 (36.7)
Obese (30+)	13 (19.4)	19 (28.4)	12 (20.0)
Treating Hospital			
Private	36 (53.7)	41 (61.2)	30 (50.0)
Public	31 (46.3)	26 (38.8)	30 (50.0)
Lymph node status			
Negative	34 (50.7)	38 (56.7)	33 (55.0)
Positive	29 (43.3)	29 (43.3)	23 (38.3)
None removed	3 (4.5)	0 (0.0)	4 (6.7)
Missing	1 (1.5)	-	-
Stage			
0	2 (3.0)	3 (4.5)	3 (5.0)
I	23 (34.3)	18 (26.9)	18 (30.0)
II/III	38 (56.7)	45 (67.2)	37 (61.7)
Unknown	4 (6.0)	1 (1.5)	2 (3.3)
Tumour Size (mm)			
median (min, max)	24.0 (6.0, 100.0)	23.0 (0.1, 82.4)	22.0 (2.2, 90.0)
Type of Surgery			
Lumpectomy	41 (61.2)	52 (77.6)	34 (56.7)
Mastectomy/MRM	26 (38.8)	15 (22.4)	26 (43.3)
Chemotherapy[a]			
Yes	41 (61.2)	42 (62.7)	34 (56.7)
No	26 (38.8)	25 (37.3)	26 (43.3)
Radiotherapy[a]			
Yes	26 (38.8)	26 (38.8)	23 (38.3)
No	41 (61.2)	41 (61.2)	37 (61.7)
Hormone therapy[a]			
Yes	42 (62.7)	38 (56.7)	34 (56.7)
No	25 (37.3)	29 (43.3)	26 (43.3)

Abbreviations:
MRM: Modified-radical mastectomy; SD: standard deviation
(a) Adjuvant therapy received over the 12-month study period

Table 3. Quality of life, function (fitness) and treatment-related side effects (fatigue) at pre-intervention (5 weeks), mid-intervention (6 months) and post-intervention (12 months) post-surgery

	Pre-intervention		Mid-intervention		Post-intervention		p-value	Δ mid-pre scores	Δ post-pre scores
	Mean	**(95% CI)**	**Mean**	**(95% CI)**	**Mean**	**(95% CI)**	**time x group interaction**	**Δ (95% CI)**	**Δ (95% CI)**
Quality of life[b]							0.030[a]		
FtF	119.4	(114.8, 123.9)	122.3	(117.1, 127.6)	128.9	(124.5, 133.4)		+2.9 (-1.2, 7.2)	+9.5[e] (5.3.3.8)
Tel	112.1	(107.4, 116.8)	120.5	(115.7, 125.2)	125.6	(120.9, 130.2)		+8.4[ef] (4.8, 11.9)	+13.5[ef] (10.0, 17.0)
UC	119.6	(114.2, 125.0)	119.5	(114.0, 124.9)	126.1	(120.8, 131.4)		-0.1 (-4.0, 3.7)	+6.5 (1.8, 11.1)
Aerobic Fitness[c]							0.016[a]		
FtF	124.0	(120.3, 127.7)	119.7	(115.6, 123.8)	115.0	(111.0, 119.0)		-4.3[f] (-8.1, -0.6)	-9.0[ef] (-12.9, -5.2)
Tel	120.9	(116.4, 125.4)	119.8	(115.5, 124.1)	114.6	(111.0, 118.2)		-1.1[f] (-4.5, 2.2)	-6.3[f] (-10.2, -2.4)
UC	115.2	(111.0, 119.4)	121.0	(115.5, 126.4)	117.9	(112.6, 123.3)		+5.8 (-0.8, 11.6)	+2.7 (-3.0, 8.4)
Fatigue[d]							0.032[a]		
FtF	36.8	(34.3, 39.3)	37.7	(34.8, 40.7)	41.7	(39.2, 44.2)		+0.9[f] (-1.5, 3.3)	+4.9 (2.6, 7.2)
Tel	33.6	(30.7, 36.4)	38.0	(35.5, 40.5)	40.4	(38.0, 42.8)		+4.4[f] (1.8, 7.1)	+6.8[e] (3.9, 9.8)
UC	37.2	(34.1, 40.3)	36.0	(33.2, 38.9)	41.8	(39.2, 44.3)		-1.2 (-3.9, 1.6)	+4.6 (1.7, 7.4)

(a) Statistically significant difference for time-effect $p < 0.05$. (b) Quality of life as measured by the FACTB+4 scale. Higher scores indicate better well-being (scale range: 0-160); change overtime or difference between groups $\geq$8 units is clinically important. (c) Aerobic fitness as assessed by heart rate on completion of modified 3-minute step test. Lower heart rate indicates better fitness; change overtime or difference between groups $\geq$1/2 standard deviation (8 beats/minute) is clinically important. (d) Fatigue as measured by the FACIT-F Questionnaire. Lower scores indicate higher levels of fatigue (scale: 0-52); change overtime or difference between groups $\geq$5 units is clinically important. (e) Clinically meaningful change over time. (f) $p \leq 0.05$ between groups compared to the usual-care group. *Abbreviations:* FtF: Face-to-face exercise group; Tel: Telephone exercise group; UC: Usual-care group.

Table 4. Effect of the exercise intervention on self-reported outcomes at pre-intervention (5 weeks), mid-intervention (6 months) and post-intervention (12-months) post-surgery

	Pre-intervention		Mid-intervention		Post-intervention		p-value
	Mean	**(95% CI)**	**Mean**	**(95% CI)**	**Mean**	**(95% CI)**	**time x group interaction**
Menopause Symptoms[c]							
Psychological scale (0-33)							0.284[a]
FtF	6.5	(5.3, 7.8)	6.3	(5.0, 7.6)	6.0	(4.8, 7.2)	
Tel	7.5	(6.2, 8.8)	7.0	(5.5, 8.4)	6.1	(5.0, 7.2)	
UC	6.1	(4.9, 7.4)	7.0	(5.7, 8.3)	5.4	(4.0, 6.9)	
Somatic scale (0-21)							0.205[a]
FtF	2.4	(1.9, 3.0)	3.3	(2.6, 4.0)	3.3	(2.5, 4.0)	
Tel	3.0	(2.4, 3.7)	3.4	(2.6, 4.1)	3.1	(2.5, 3.7)	
UC	2.4	(1.9, 2.9)	3.1	(2.3, 3.9)	3.4	(2.7, 4.1)	
Vasomotor scale (0-6)							0.356[ab]
FtF	0.6	(0.3, 0.9)	2.2	(1.7, 2.7)	1.8	(1.4, 2.3)	
Tel	1.3	(0.9, 1.7)	2.6	(2.1, 3.1)	2.4	(1.9, 2.9)	
UC	1.0	(0.6, 1.4)	1.9	(1.4, 2.4)	1.9	(1.3, 2.4)	
Neuropathic pain[d] (0-100)							0.441[a]
FtF	18.0	(13.8, 22.2)	16.0	(11.3, 20.7)	13.0	(8.7, 17.3)	
Tel	20.4	(16.0, 24.9)	12.3	(8.4, 16.1)	12.2	(8.2, 16.2)	
UC	18.1	(13.6, 22.6)	11.7	(7.2, 16.1)	11.4	(7.4, 15.5)	
Upper-body function, patient-reported[e]							0.056[a]
FtF	17.9	(14.1, 21.7)	12.3	(7.8, 16.7)	10.2	(6.5, 14.0)	
Tel	24.5	(20.2, 28.8)	12.3	(9.3, 15.3)	11.0	(8.3, 13.7)	
UC	20.4	(16.4, 24.3)	14.9	(10.9, 18.8)	13.6	(9.8, 17.4)	
Upper-body function, clinically measured[f]							0.057[ab]
FtF	7.3	(6.7, 7.9)	8.9	(8.2, 9.6)	9.2	(8.6, 9.8)	
Tel	6.8	(6.1, 7.5)	8.1	(7.4, 8.7)	8.3	(7.8, 8.8)	
UC	6.3	(5.4, 7.2)	6.9	(6.0, 7.8)	8.0	(7.1, 9.0)	

(a) Statistically significant difference for time-effect $p < 0.05$. (b) Statistically significant difference for group-effect $p < 0.05$. (c) Menopause symptoms as measured by the Greene Climacteric Scale. Higher scores indicate greater menopausal symptoms; change overtime or difference between groups $\geq$1/2 standard deviation ($\geq$7.5 units) is clinically important. (d) Neuropathic Pain Scale. Higher scores indicate higher levels of pain; change overtime or difference between groups $\geq$1/2 standard deviation ($\geq$9 units) is clinically

important. (e) Patient-reported upper-body function as measured by the DASH scale. Higher scores indicate worse function; change overtime or difference between groups ≥1/2 standard deviation (≥7.5 units) is clinically important. (f) Clinically measured upper-body function as measured by strength and endurance test. Higher scores indicate better functioning; change overtime or difference between groups 1.5 stages is clinically important. *Abbreviations:* FtF: Face-to-face exercise group; Tel: Telephone exercise group; UC: Usual-care group.

Table 5. Proportion of women with lymphoedema, anxiety, depression and gains in body mass index at baseline, mid-intervention (6 months post-surgery) and post-intervention (12 months post-surgery)

	Baseline		Mid-intervention		Post-intervention	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Lymphoedema						
Self-report of a clinical diagnosis						
FtF	2	(3.2)	4	(6.9)	5	(8.9)
Tel	1	(1.5)	6	(10.3)	2	(3.3)
UC	2	(3.6)	5	(10.2)	4	(8.2)
Objectively-measured[a]						
FtF	1	(1.5)	4	(6.5)	8	(13.1)
Tel	1	(1.5)	4	(6.6)	8	(12.9)
UC	0	(0.0)	6	(10.7)	9	(16.4)
Clinically anxious[b]						
FtF	2	(3.5)	1	(1.6)	2	(3.3)
Tel	2	(3.4)	5	(8.3)	2	(3.3)
UC	0	(0.0)	2	(3.6)	3	(5.5)
Clinically depressed[c]						
FtF	1	(1.7)	2	(3.3)	0	(0.0)
Tel	2	(3.4)	4	(6.6)	0	(0.0)
UC	1	(2.0)	2	(3.6)	2	(3.6)
>1 body mass index unit change from baseline						
FtF			13	(21.0)	11	(18.0)
Tel			16	(26.2)	22	(34.5)
UC			13	(24.1)	13	(24.1)

(a) Objectively-measure lymphoedema as measured by BIS; a participant was classified as having lymphedema when the L-Dex score was $\geq$10. (b) Clinically anxious as measured by the Greene Climacteric Scale; women reporting scores of >10 for scale items 1-6 were classified as clinically anxious. (c) Clinically depressed as measured by the Greene Climacteric Scale; women reporting scores of >10 for scale items 7-11 were classified as clinically depressed. *Abbreviations:* FtF: Face-to-face exercise group; Tel: Telephone exercise group; UC: Usual-care group.