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Effects of the ACTIVity And TEchnology (ACTIVATE) intervention on health-related quality of life and fatigue outcomes in breast cancer survivors

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Manuscript title: Effects of the ACTIVity And TEchnology (ACTIVATE) intervention on health-related quality of life and fatigue outcomes in breast cancer survivors.

Running title: Patient reported outcomes from the ACTIVATE Trial

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ABSTRACT

Background: The ACTIVATE Trial examined the efficacy of a wearable-based intervention to increase physical activity and reduce sedentary behaviour in breast cancer survivors. This paper examines the effects of the intervention on health-related quality of life (HRQoL) and fatigue at 12 weeks (T2; end of intervention) and 24 weeks (T3; follow-up).

Methods: Inactive and postmenopausal women who had completed primary treatment for stage I-III breast cancer were randomized to intervention or waitlist control. Physical activity and sedentary behaviour were measured by Actigraph® and activPAL™ accelerometers at baseline (T1), end of the intervention (T2), and 12 weeks follow up (T3). HRQoL and fatigue were measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). Primary intervention effects were evaluated comparing intervention and waitlist group at T2 using repeated measures mixed effects models.

Results: Overall, 83 women were randomized and trial retention was high (94%). A 4.6-point difference in fatigue score was observed between groups at T2 (95% CI: 1.3, 7.8) indicating improvement in fatigue profiles in the intervention group. In within groups analyses the intervention group reported a 5.1-point increase in fatigue from baseline to T2 (95% CI: 2.0, 8.2) and a 3.3-point increase from baseline to T3 (95% CI: 0.1, 6.41).

Conclusions: Despite small improvements in fatigue profiles, no effects on HRQoL were observed. While the ACTIVATE Trial was associated with improvements in physical activity and sedentary behaviour, more intensive or longer duration interventions may be needed to facilitate changes in HRQoL.

INTRODUCTION

Several epidemiological studies have suggested that physically active breast cancer survivors have a lower risk of recurrence, and overall and cancer specific mortality, compared to those survivors who are inactive.[1] Interventions have also consistently concluded physical activity has small-to-moderate beneficial effects on patient reported outcomes after adjuvant therapy for breast cancer including fatigue and health-related quality of life (HRQoL).[2] Despite these findings, research suggests that the majority of breast cancer survivors are not meeting public health recommendation for physical activity (i.e., at least 150 min of at least moderate intensity activity per week, or 75 minutes of vigorous intensity activity per week), and most waking hours are spent in sedentary pursuits.[3,4]

Exercise interventions for breast cancer survivors have demonstrated significant improvements in physical activity, and other outcomes including HRQoL, physical and social function, and cardiorespiratory fitness.[2] Given the high cost, and limited reach and availability of such programs, several interventions have examined broad-reaching approaches (e.g., telephone, web/online, print, smartphone, oncologist-delivered).[5] Several of these interventions include behavioural support strategies including goal-setting, feedback, and self-monitoring. However, a recent systematic review and meta-analysis of these studies concluded intervention effects were small, and few studies examined interventions utilizing mobile and electronic health platforms (i.e., mHealth and eHealth).[5]

In the general population, consumer-based wearable activity trackers have shown promise as a potential mode in which to facilitate physical activity.[6] A small number of studies have tested wearable activity trackers in the cancer context, and several are currently underway.[7] Breast cancer survivors have indicated wearable activity trackers are a useful, preferred, and acceptable mHealth approach to facilitate behaviour change,[5] and studies implementing these devices are now starting to emerge. We recently completed the ACTIVity And TEchnology (ACTIVATE) Trial,[8] an intervention that examined the efficacy of a wearable technology-based intervention (using the Garmin Vivofit 2®, with a behavioral feedback and goal setting session, and five telephone-delivered health coaching sessions). We reported that the intervention successfully increased moderate to vigorous physical activity (MVPA) (between group change =

69 minutes/week, 95% CI: 22, 116) and decreased sitting time (-37 minutes/day, 95% CI: -72, -2),[9] and the MVPA changes were sustained three months after the intervention.[10]

Interventions with cancer survivors using wearable technology have focused on behaviour change outcomes,[11,12] yet few have reported mobile health (mHealth) interventions effects on cancer-related outcomes. The primary aim of this paper was to report the ACTIVATE Trial effects on patient-reported outcomes including health-related quality of life (HRQoL) and fatigue.

METHODS

The ACTIVATE Trial protocol was approved by Cancer Council Victoria's Human Research Ethics Committee (HREC-1602). The trial design and protocol have been described,[8] and below we outline the methods.

Participants and recruitment

Participants in the ACTIVATE Trial were inactive and postmenopausal at the time of diagnosis with stage I-III breast cancer and had completed treatment (ongoing hormone therapy was permitted). Participants had daily access to a smart phone, mobile device, or personal computer with internet, and during telephone screening reported less than 75 minutes of MVPA per week and more than seven hours of sedentary behaviour per day. Participants were recruited via a range of convenience methods.

The main method for recruitment was via Register4 and the Breast Cancer Network of Australia's Review and Survey Group, two national registers of volunteers who had indicated their interest in participating in cancer research. Other recruitment strategies included placement of paid advertisements on Facebook® and promotion through newsletters published by Counterpart (a Melbourne-based not-for-profit group supporting women diagnosed with breast and gynecological cancer), the National Breast Cancer Foundation (a national breast cancer charity), and Cancer Council Victoria. Finally, posters and promotional postcards were sent to Melbourne oncology clinics and general practice clinics. Women who enquired about the ACTIVATE Trial were administered a brief, telephone delivered screening questionnaire to confirm their eligibility. Recruitment was conducted between July 2016 and July 2017.

Intervention

The primary intervention was composed of three components, delivered over a 12-week period. Intervention participants received: 1) behavioral feedback and goal-setting in a single face-to-face session at Cancer Council Victoria with two trained ACTIVATE Trial research assistants, 2) a wrist-worn Garmin Vivofit2® activity monitor which they were asked to wear for 12 weeks, and 3) five telephone-delivered behavioral counselling sessions (the first two calls were weekly, followed by two calls made a fortnight apart, and a final call one month later) from a trained research assistant. All ACTIVATE research assistants had qualifications in Kinesiology

or Health Promotion and received several training sessions prior to the Trial by experienced implementation support staff with expertise in physical activity and health promotion.

During the 12-week maintenance phase (T2 to T3), intervention group participants retained their Garmin Vivofit2® but its use was discretionary.

Waitlist control arm (abridged intervention)

Participants randomized to the waitlist control arm were informed that they were randomized to a delayed intervention and were provided with a Garmin Vivofit 2® in approximately three months (in a face-to-face meeting), following the second data collection time point (T2). The abridged intervention was also 12 weeks in length. After waitlist control arm participants completed their T2 data collection, they attend a short meeting with a Trial team member, who provided the same training in the set up (including downloading and installing the smartphone/tablet/PC application), calibration, and use of the Garmin Vivofit 2® that the primary intervention group receive. Participants were also provided with the instruction booklet for their activity monitor. Participants did not receive any behavioural feedback, goal setting or phone calls.

Data collection

Participants were mailed the baseline (T1) assessment package: a study information sheet and consent form; an Actigraph® GT3X+ accelerometer (Actigraph, Pensacola, FL) on an

elasticized waist band; an activPAL™ (PAL Technologies Limited, Glasgow, UK) and several 3M™ Tegaderm™ transparent dressings to adhere the device to the thigh; written instructions on how to wear each accelerometer; a diary to record accelerometer wear across the seven days; a written baseline questionnaire; and a reply-paid envelope to return these materials. The follow-up data collection package (containing the same items, except for a modified follow-up questionnaire) was mailed to all participants at the end of the 12-week primary intervention period for intervention group or waiting period for control group (T2) and end of the second 12-week period of abridged intervention for waitlist control group or maintenance period for intervention group (T3). The Actigraph® GT3X+ accelerometer data were downloaded and processed using 60-second epochs, using the ActiLife 6.0 software package. We used the Sasaki vector magnitude cut point (utilizing tri-axial data) of ≥2,690 cpm to quantify MVPA.[13] Sitting time was assessed by the activPAL™, which participants were asked to wear 24 hours/day.

Health-related quality of life was measured at all three timepoints using the Functional Assessment of Cancer Therapy-Breast (FACT-B)[14] and fatigue was measured with the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).[15] The FACT-B is a 37-item scale that contains physical, social, emotional, and functional well-being subscales (these four subscales comprise the FACT-General), in addition to a 10-item breast cancer-specific subscale focused on concerns about body image, shortness of breath, and pain. The FACIT-F includes 13 items, such as ‘I feel fatigued’ and ‘I feel weak all over’. Items are scored on a range from 0 to 52 with higher scores indicating better quality of life or less fatigue. We also calculated

the Trial Outcome Index (TOI); a summary index of physical/functional outcomes that is generated by summing the physical and functional subscales with the 'additional concerns' subscale.[16] Our findings were judged based on established clinically important differences specific to the FACT-B and FACIT-Fatigue scales.[17] The FACT-B and FACIT-Fatigue are widely used measurement tools that have established evidence of internal consistency, test–retest reliability, and convergent and discriminant validity.[14]

Statistical analysis

Primary intervention effects on HRQoL and fatigue were evaluated by comparing intervention and waitlist group at T2 using repeated measures mixed effects models. Fixed effects included in models were time (i.e., T1 and T2), group (i.e., Intervention and Waitlist) and their interaction. A random intercept was included to account for variances between and within participants. Primary intervention effects on HRQoL and fatigue were evaluated by comparing intervention and waitlist group at T2 using repeated measures mixed effects models on intention-to-treat basis. Our primary analysis was unadjusted, but we also computed analyses adjusted for baseline values of age, marital status, education, income, smoking status, BMI, cancer stage, cancer treatment, and number of comorbidities. To determine clinically important differences, our between group difference values were compared to previously established thresholds (e.g., FACIT-Fatigue = 3.0 points).[15] All analyses were carried out using Stata version 14 (Statacorp, College Station, TX, USA).

RESULTS

Sociodemographic and medical characteristics of the sample are presented elsewhere. Flow of participants through the trial is shown in Figure 1. Overall, 83 women were randomized, and trial retention was high since 78 women completed T2 assessments (94%). Mean age of the sample was 62 years (6.4), mean BMI was 29 (6.0), and 43% received surgery with two adjuvant therapies. We previously reported good compliance with the intervention.[9] Overall, 68% of participants received all five telephone calls, while 25% received four and three participants received three calls. The average Actigraph® wear time at T1 was 820 min/day (intervention arm) and 837 min/day (waitlist control arm); at T2 it was 832 min/day (intervention arm) and 846 min/day (waitlist control arm), respectively.[7]

Twelve-week intervention results are located in Table 1, and maintenance/abridged intervention results are located in Table 2. Based on linear mixed model analyses, a 4.6-point difference in fatigue score was observed between groups at T2 (95% CI: 1.3, 7.8) indicating improvement in fatigue profiles in the intervention group. There were no other statistically significant differences between groups on the HRQoL variables. There were no between group differences in other HRQoL outcomes (i.e., FACT-B Trial Outcome Index, FACT-Breast, FACT-General). Results remained significant for fatigue score and insignificant for HRQoL variables after adjustment (data not presented).

In the maintenance/abridged intervention phase, the improvements in fatigue in the intervention group were slightly attenuated during the maintenance phase (see Table 2). There

were some improvements in both the intervention and waitlist control group for TOI. The intervention group reported a small 1.9-point improvement between T2 to T3, making the total improvement for TOI across the intervention and maintenance phase a significant 3.7-point (95% CI: 0.6, 6.9) improvement. The control group had a 1.6-point increase (T2 to T3) and 3.6-point (95% CI: 1.1, 6.1) overall improvement in TOI from T1 to T3.

Table 3 shows the percentage of intervention and waitlist control participants achieving a clinically important difference on the TOI, FACIT-Fatigue, and FACT-B scales. The most notable improvement was seen for fatigue where 60.5% of intervention participants reported a clinically relevant improvement and 27.5% of waitlist control participants reported a clinically important difference from T1 to T2. Figures 2 and 3 illustrate the fatigue and HRQoL scores at baseline (T1), 3 months (T2) and 6 months (T3) for the intervention and waitlist groups, respectively.

DISCUSSION

The ACTIVATE Trial intervention conducted in breast cancer survivors that used wearable technology, telephone coaching, and goal-setting, increased MVPA and reduced total sitting time. Despite these changes, the current analyses suggest the intervention was not associated with strong improvements in patient reported outcomes. The lack of intervention effects may have been due to the small sample size, and contamination in the waitlist control group as demonstrated by small increased in physical activity in the waitlist control group.[9]

However, a meaningful reduction in fatigue following delivery of the primary intervention was observed with some maintenance of the improvement during follow-up post-intervention. The strengths of this study include the high rate of retention (94%) and adherence to the intervention, the abridged intervention, and the inactive and sedentary sample of survivors. Use of Actigraph® and activPAL™ devices to measure our outcome variables captured the postural aspects of sitting (via activPAL™) and reduced the measurement error that is associated with self-reported estimates of physical activity and sedentary behavior.

We found no between group differences in any of the HRQoL outcomes. Few randomized controlled trials examining distance-based approaches to promoting physical activity in cancer survivors have used wearable activity trackers.[5] Only a few studies testing wearables have reported patient reported outcomes such as HRQoL and fatigue.[11,18,19] For example, in one randomized trial of African American breast cancer survivors (N=35),[18] survivors were randomized to either a FitBit device combined with access to a web-based health platform (SparkPeople) group, or a waitlist control group. At both three and six months, no differences in QoL were observed between the groups (using the Quality of Life in Adult Cancer Survivors Scale). In another trial, 46 prostate cancer survivors received a Jawbone UP 24 activity tracker.[19] No statistically significant effects on HRQoL (using the FACT scales) were observed at either 12-week or 24-week follow up. Finally, McNeil and colleagues randomized 45 breast cancer survivors to a home-based exercise program that included a Polar A360(R) activity tracker combined with goal-setting and follow-up phone calls.[11] Similar to our results, participants

reported increases in MVPA and reduced sedentary time, but no changes in both generic (SF-12) or disease-specific (using the FACT scales) HRQoL. Our data are consistent with these aforementioned studies and suggest that short term interventions (e.g., 12 weeks) using wearable activity trackers, despite demonstrating favorable behaviour change, may not be sufficiently long to improve HRQoL and/or other patient reported outcomes.

The ACTIVATE Trial intervention was associated with a statistically significant reduction in fatigue profiles. The 4.6-point reduction in fatigue scores met and exceeded the 3.0-point threshold for determining a minimal clinically important difference;[15] defined as the smallest benefit that is of value to patients.[20] Currently, there are no other wearable activity tracker-based interventions in the cancer context that have examined effects on fatigue. Cancer-related fatigue is one of the most commonly report and most distressing side effect of breast cancer and related treatment(s).[21] The TOI improvements observed in the abridged intervention did not approach the clinically important difference threshold of 5.0 points.[13] Based on our study, wearable activity trackers combined with other behavioural supports (e.g., telephone counseling and goal setting) may be one promising intervention that could assist in reducing fatigue symptoms in the short term. While the observed changes are small due to the 12-week follow up, future research should examine approaches to increase the magnitude of changes in these outcomes.

STUDY LIMITATIONS

The limitations of this study include the small sample size, the relatively homogenous sample, the short intervention period and the lack of assessment of all aspects of patient reported outcomes (e.g., depression) and physical measurements.

CLINICAL IMPLICATIONS

Currently, there are an increasing number of methods papers describing randomized controlled trials examining the role of wearable activity trackers in the cancer context that indicate an uptake in research in this area.[22,23] Future interventions examining wearable activity trackers should report not only behavioural outcomes (e.g., physical activity, sedentary time), but clinical (e.g., body mass index, cardiorespiratory fitness) and patient reported (e.g., HRQoL, fatigue, depression) outcomes as well. Such interventions will lend to a better understanding of the role of wearable activity trackers in cancer survivorship. This study adds to the growing evidence base that objectively measured physical activity done after treatment in breast cancer survivors is associated with decreased fatigue levels. This evidence adds support to clinical recommendations for cancer survivors to incorporate physical activity as part of their post-treatment rehabilitation and recovery plan.

CONCLUSIONS

While the ACTIVATE trial was associated with improvements in physical activity and sedentary time, the current analyses suggest the intervention was not associated with meaningful improvements in HRQoL. The ACTIVATE Trial intervention was associated with a statistically significant reduction and clinically important difference in fatigue profiles.

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Table 1. Between-group changes in fatigue and health-related quality of life from baseline to end of intervention in the ACTIVATE Trial, 2016-2017.

Patient Reported Outcome[a]		Baseline[b]	End of intervention[c]	Mean between groups difference (95% CI)	Time x Group[d]
FACIT-Fatigue score (0-52)					
	Intervention	33.2 (10.3)	38.0 (8.9)	4.6 (1.3, 7.8)	**0.007**
	Waitlist control	37.2 (10.1)	37.7 (11.1)		
FACT-Breast Cancer Subscale (0-40)					
	Intervention	24.5 (5.6)	25.5 (5.8)	0.1 (-1.8, 2.0)	0.915
	Waitlist control	24.2 (4.6)	24.9 (4.7)		
FACT-B Trial Outcome Index (0-96)					
	Intervention	63.5 (15.0)	66.1 (16.2)	0.8 (-3.1, 4.7)	0.697
	Waitlist control	65.7 (12.2)	67.3 (13.4)		
FACT-General (0-108)					
	Intervention	75.4 (18.7)	77.8 (20.3)	1.3 (-3.4, 6.0)	0.595
	Waitlist control	79.4 (15.5)	80.5 (16.7)		
FACT-B Total (0-148)					
	Intervention	100.0 (22.3)	103.5 (24.5)	1.4 (-4.3, 7.1)	0.636
	Waitlist control	103.6 (17.8)	105.5 (20.2)		

[a] The higher the score, the better the HRQoL.

[b] Baseline data (T1) based on all study participants (N=83)
[c] Data based on participants completed postintervention assessment (T2) (N=78)
[d] p-value of "Time x Group" interaction from Unadjusted linear mixed models for T1-T2 between group differences.
Repeated measures mixed model with fixed effects include assessment time (T1 vs. T2), study group and their interaction. Mean change scores may not precisely reflect postintervention minus baseline score given that means are model fitted.

Table 2. Within-group changes in fatigue and health-related quality of life from baseline to end of intervention in the ACTIVATE Trial, 2016-2017.

	Intervention group			**Wait list control arm**		
Patient Reported Outcome	Baseline to end of intervention	End of intervention to follow up	Baseline to follow up	Baseline to end of intervention	End of intervention to follow up	Baseline to end of intervention
FACIT-Fatigue score (0-52)	5.1 (2.0, 8.2); **0.002**	-0.9 (-3.2, 1.5); 0.452	3.3 (0.1, 6.41); **0.04**	0.5 (-1.2, 2.1); 0.581	0.4 (-1.8, 2.6); 0.699	1.0 (-0.6, 2.7); 0.221
FACT-Breast Cancer Subscale (0-40)	0.8 (-0.7, 2.3); 0.291	0.3 (-1.1, 1.7); 0.672	1.3 (-0.3, 2.8); 0.107	0.8 (-0.5, 2.0); 0.248	-0.3 (-1.5, 0.9); 0.603	0.8 (-0.6, 2.3); 0.258
FACT-B Trial Outcome Index (0-96)	2.3 (-1.2, 5.9); 0.195	1.9 (-1.3, 5.0); 0.244	3.7 (0.6, 6.9); **0.02**	1.6 (-0.6, 3.8); 0.146	1.6 (-0.8, 3.9); 0.176	3.6 (1.1, 6.1); **0.006**
FACT-General (0-108)	2.4 (-1.9, 6.7); 0.271	0.6 (-3.4, 4.5); 0.777	2.4 (-0.9, 5.7); 0.158	1.1 (-1.5, 3.7); 0.406	2.5 (-0.4, 5.4); 0.084	3.4 (-0.1, 6.8); 0.06
FACT-B Total (0-148)	3.2 (-1.9, 8.2); 0.217	1.0 (-3.7, 5.6); 0.68	3.6 (-0.5, 7.8); 0.087	1.8 (-1.5, 5.2); 0.271	2.2 (-1.1, 5.5); 0.176	4.1 (-0.1, 8.2); 0.06

*Repeated measures mixed models with within-subject random factor [mean of change, (95%CI), p-value].

Table 3. Percentage of participants achieving clinically important differences in fatigue and health-related quality of life in the ACTIVATE Trial, 2016-2017.

	% achieving clinically important difference (from T1-T2)		**% achieving clinically important difference (from T1-T3)**	
Patient reported outcome	Intervention	Waitlist control	Intervention	Waitlist control
FACIT-Fatigue score (CID* of 3)	60.5%	27.5%	47.1%	38.8%
FACT-Breast Cancer Subscale (CID of 7)	35.2%	34.3%	29.4%	34.3%
FACT-B Trial Outcome Index (CID of 5)	32.54%	27.5%	41.2%	41.2%

*CID=clinically important difference

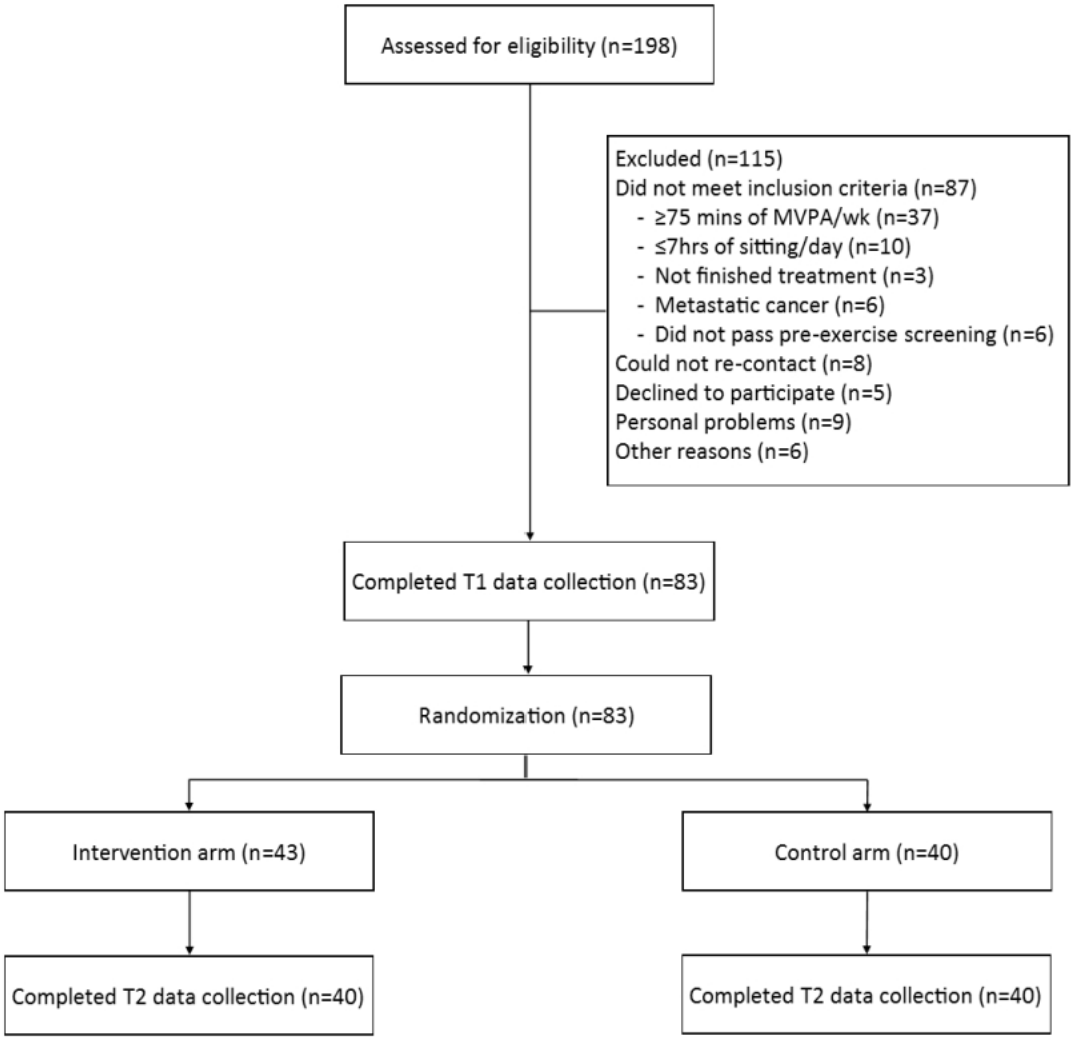
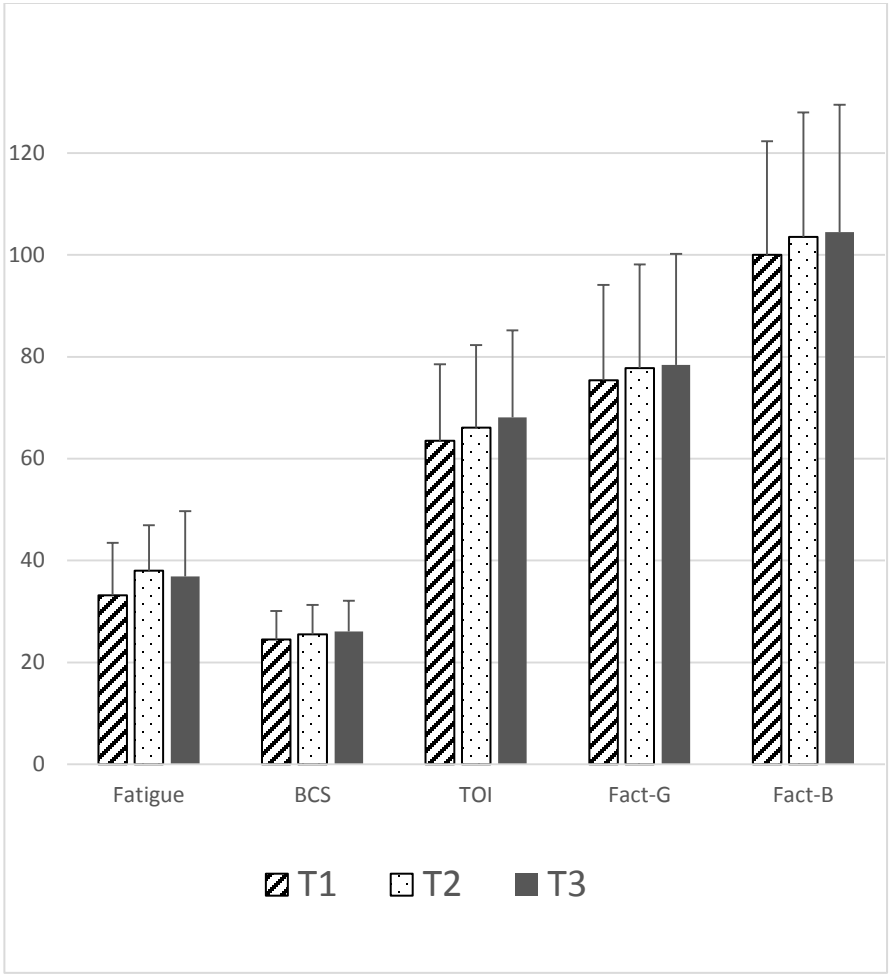


Figure 1. Flow of participants through the ACTIVATE trial



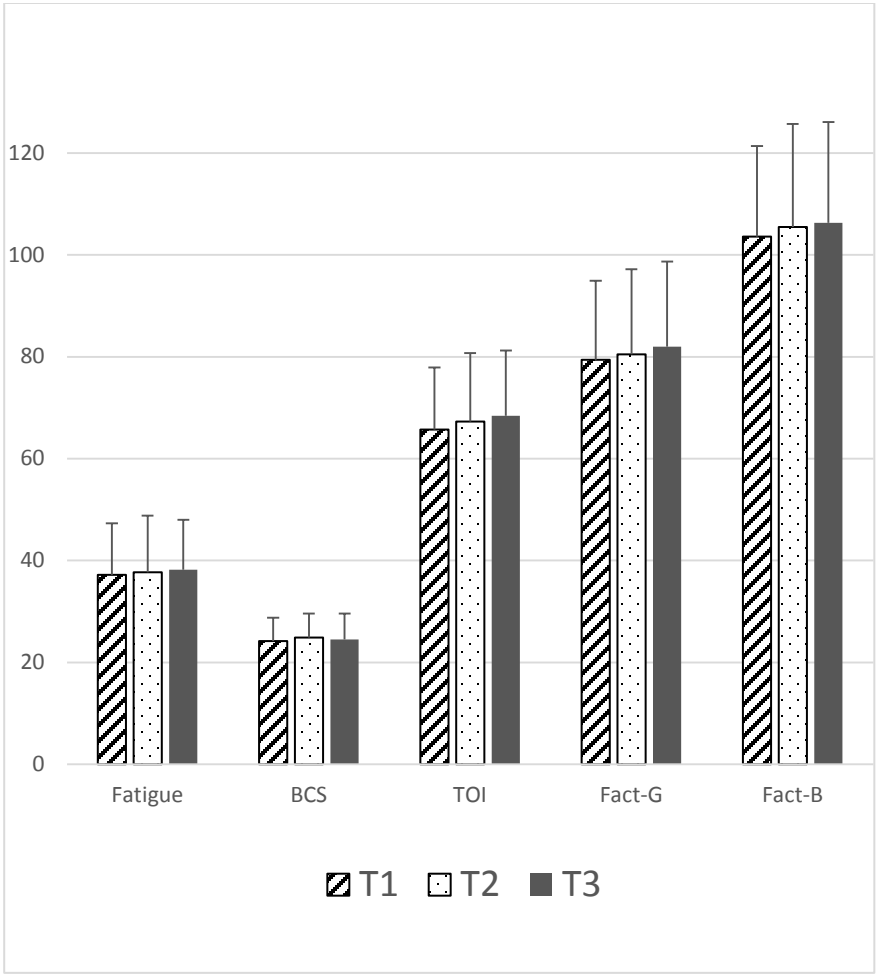


Figure 2. Mean scores of Fatigue and HRQoL scales at baseline (T1), 3 months (T2) and 6 months (T3) of intervention group

Figure 3. Mean scores of Fatigue and HRQoL scales at baseline (T1), 3 months (T2) and 6 months (T3) of waitlist group