

## STUDY PROTOCOL

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# Can physical activity help to maintain cognitive functioning and psychosocial well-being among breast cancer patients treated with chemotherapy? A randomised controlled trial: study protocol

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## Abstract

**Background:** Evidence suggests chemotherapy treatment for breast cancer is associated with side effects such as cognitive impairment in domains of memory, attention, concentration and executive function. Cognitive impairments reported by patients have been associated with higher levels of emotional distress. To date, intervention studies to alleviate cognitive impairment associated with chemotherapy have focused on psycho-educational techniques or cognitive training. Studies have not yet considered physical activity as a potential for alleviating cognitive problems. Physical activity interventions are reported to be effective in alleviating emotional distress and fatigue in those with breast cancer. They have also been reported to improve cognitive functioning in the elderly, in those suffering with dementia and in children. We propose that physical activity could also help to alleviate cognitive impairments in women diagnosed with breast cancer. The study has been designed using a recently developed taxonomy of behaviour change techniques to reliably report the content of the intervention to allow future replication.

**Method:** This study will deliver a home-based moderate intensity walking intervention to women diagnosed with breast cancer mid-way through their chemotherapy treatment and will compare them to patients receiving usual care alone. The primary outcome measure for this intervention is changes in an objective measure of memory assessed using the Digit Span. Secondary outcome measures include: objective measures of executive function; attention; visual spatial skills; self report cognitive function; self-report fatigue; anxiety; depression; mood and self-esteem. As emotional distress has been associated with self-reporting of cognitive problems, this intervention will further test whether emotional distress mediates between the amount of walking undertaken during the intervention period and levels of self-reported cognitive functioning.

**Discussion:** The development of an effective intervention for preventing difficulties in emotional and cognitive functioning of cancer patients' post-treatment will help to guide health care professionals to improve patients' overall quality of life. It will also provide direction for future research, ultimately to improve the day to day functioning of breast cancer survivors.

**Trial Registration:** Current Controlled Trials ISRCTN50709297.

**Keywords:** Intervention, Breast cancer, Chemotherapy, Physical activity, Exercise, Walking, Cognitive function, Emotional distress, Psychosocial well-being

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## Background

Breast cancer is one of the most frequently diagnosed cancers in the UK [1]. Between 15% to 75% of patients treated by chemotherapy experience problems with their cognitive functioning as well as physical and emotional side effects [2,3]. Multiple cross-sectional and longitudinal studies over the last decade have found associations between chemotherapy and cognitive impairments, both subjectively reported and objectively measured, in a proportion of breast cancer patients and survivors [4-10]. Commonly reported cognitive impairments include difficulties with memory, attention, information-processing speed and executive function [11,12]. Studies suggest that around 71% of patients report problems with memory and 64% report difficulties with concentration [13,14]. In addition, patients receiving chemotherapy were 2.25 times more likely to show cognitive decline following chemotherapy in comparison with the control group [13]. The effects of chemotherapy on cognitive function among breast cancer patients can be long-term with impairments evident between 4 months to 20 years post-treatment [15-19]. Cognitive decline following chemotherapy for breast cancer can have a profound negative impact on patients' overall quality of life [13,15,20,21].

Evidence suggests that cognitive problems are more frequently reported by patients than that objectively measured using neuropsychological assessments. Literature suggests that subjective reporting and objective measurements of cognitive decline are not associated with one another [5,6,9,10,22-27] but both are associated with poorer functional outcomes and psychosocial well-being, which may be a predisposing risk factor for developing cognitive impairment following chemotherapy in those with breast cancer. [5,6,13,20,22,23,25,26,28-34].

The above studies suggest the need for evidence-based interventions to prevent cognitive decline experienced by breast cancer patients during chemotherapy. However, very few interventions have been implemented to address cognitive difficulties and have yielded mixed results. For example, Poppelreuter et al. [35] found no intervention effects through the implementation of cognitive training strategies whereas Von Ah et al. [36], who also used cognitive training, reported improvements in self-reported cognitive functioning, better mental health and quality of life outcomes. Ferguson et al. [37] implemented a cognitive behavioural therapy intervention and found no significant effect on self-reported cognitive function [37]. Schuurs et al. [38] delivered a psycho-education programme on cognitive strategies by using goal setting and problem solving techniques. They found positive improvements in the management of objective and subjective cognitive function, psychosocial distress and social functioning in patients with a range of cancer diagnoses [38].

The interventions discussed above were implemented between 12 to 8 months after the completion of treatment. However, evidence suggests that patients report difficulties with cognitive functioning half way through their treatment [39,40]. Evidence suggests that interventions to manage the side effects of chemotherapy would be beneficial to patients mid way through treatment as 75% of patients experience cognitive decline during treatment with 35% of patients continuing to report cognitive problems post-treatment [41]. Therefore, more efforts should be made towards preventing cognitive problems during treatment when it is most prevalent.

The benefits of physical activity among cancer patients are well documented with regards to managing treatment related symptoms such as fatigue, regaining physical functioning, improving quality of life [42,43] and for improving physical functioning and fitness for breast cancer patients [44-51]. A meta-analysis of 28 studies revealed positive effects of exercise on cancer related fatigue both during and after treatment [52]. Physical activity reduced distress and improved fatigue and energy levels at three month follow up [51-53]. Physical activity rehabilitation has also shown to improve levels of anxiety for those affected by breast cancer [54]. Evidence demonstrates promising effects of low to moderate levels of physical activity as a protective strategy for preventing cognitive impairment in healthy individuals, children and the elderly [55-59]. In light of this evidence we hypothesise that moderate levels of physical activity may also help in protecting breast cancer patients against chemotherapy-induced cognitive impairment. Hospital-based and/or supervised interventions can restrict participation as patients undergoing chemotherapy are often busy with treatment schedules, are unwell or have limited access to exercise facilities due to transportation or scheduling difficulties [44]. Therefore, home-based interventions which do not restrict participation may be more feasible and increase adherence.

To summarise, there is good evidence illustrating the benefits of physical activity rehabilitation for cancer patients. However, the effects of physical activity on cognitive functioning for those diagnosed with cancer have not yet been examined. Current studies implementing physical activity as a form of rehabilitation for breast cancer have focused upon the benefits it has on physical fitness, quality of life, fatigue and emotional distress. Very little research has been conducted to explore the effects of physical activity upon cognitive functioning in breast cancer patients. Therefore, the current intervention aims to investigate the effects of a self-prescribed moderate intensity walking on cognitive functioning and emotional well-being of adjuvant and neo-adjuvant breast cancer patients.

## Methods

### Objectives/hypothesis

The primary aim of the study is to investigate the effectiveness of a home-based moderate intensity walking intervention on reducing cognitive impairment of breast cancer patients receiving chemotherapy. Our primary hypothesis is that women who complete the physical activity intervention will demonstrate less impairment in memory in comparison to women in the non-intervention group. Our secondary hypotheses are that the intervention group will perform better than the control group on objective and subjective measures of cognitive function, and will report better quality of life outcomes than the control group. Furthermore, within the intervention group, emotional well-being will mediate between physical activity level and level of subjectively reported and objectively tested impairment in memory, attention and concentration.

### Design

The study is a randomised controlled trial comparing the home based walking intervention group with care as usual control group. Outcomes will be assessed at two time points: mid-way through chemotherapy (pre-intervention) and after the completion of chemotherapy (post-intervention). All participants will also complete outcome measures prior to receiving chemotherapy to familiarise them with study materials, study setting and the researcher.

### Recruitment

Sixty two females with a primary diagnosis of breast cancer will be recruited from the Leicester Royal Infirmary (31 participants per group). Patients who have been diagnosed, are waiting to begin adjuvant or neo adjuvant chemotherapy and are considered fit to take part in moderate intensity exercise by their oncologist will be invited to participate in the study by the researcher. Oncologists will subjectively assess patients' suitability for the study based upon their medical history and physical presentation during the consultation. Those interested in participating then meet with the researcher who will provide them with an information sheet and explain the study in further detail. Those participants who show interest are then followed up a week later at which point they are asked to complete a consent form. Participants will be assessed using objective measures of cognitive functioning in a small room near the waiting area. They will also complete a series of self-report questionnaires in the comfort of their own homes and return them using the pre-paid envelope provided.

### Inclusion criteria

The researcher will assess patients to ensure they meet the following inclusion criteria: to be female; aged 18–75

at diagnosis; have a primary diagnosis of stage I to III breast cancer; receiving chemotherapy and are able to speak and read English.

### Exclusion criteria

Patients will not be eligible for the intervention if they meet the following exclusion criteria: previously diagnosed with cancer; those who currently exceed the recommended guidelines of 30 minutes of moderate intensity exercise five times a week; breast cancer is a secondary diagnosis and have a current psychiatric disorder.

### Randomisation

Eligible participants will be block randomised using four blocks to ensure equal numbers of patients in both groups as recruitment will be staggered. Within each group of four patients, two will be allocated to the intervention group and two to the control group at time two (mid way through chemotherapy). There is no masking of participants or the research team.

### Intervention

In line with previous literature [60] the intervention will consist of 12 weeks of home-based moderate intensity walking compared with usual care alone. The researcher will provide patients with an intervention booklet which will include: guidance and recommendations to ensure adherence to the intervention; tips and encouragement outlining the benefits of walking; and a diary to keep a log of walking duration and intensity.

In line with recommended guidelines [61], participants will be asked to exercise for 30 minutes five times a week at moderate intensity (defined as walking at a brisk pace). Participants will be encouraged by the researcher to gradually increase walking duration from 10 to 30 minute bouts through the course of the intervention and will be asked to make weekly goals outlining intended exercise intensity, duration and timing (exactly when they intend to exercise). They will be encouraged to reflect upon their achievements or shortfalls from the previous week and to take these into consideration by modifying their goals to ensure they are realistic and achievable. They will also be asked by the researcher to take their chemotherapy schedule into consideration, in order to ensure that they do not over exert themselves or set unrealistic goals during weeks in which they will be receiving treatment. This information will also be presented in the walking booklet. Pedometers will be given to the intervention group at the start of the intervention so that they can be used to measure daily step count and to provide patients with immediate feedback and motivation. Relevant behaviour change taxonomies [62] have been applied to this design in order to allow accurate, reliable replication (Table 1).

**Table 1 Definitions of behaviour taxonomy [51] and application to intervention**

Behaviour change technique number and label	Definition of BCT	Materials	Summary (use of technique in intervention)
<b>Social support</b>			
1. Social support (unspecified)	Advise on, arrange or provide social support or non-contingent praise or reward for the behaviour.	Intervention booklet	Participants received intervention booklets outlining the benefits of walking during treatment, advising them to increase levels of walking and encouraging them to walk with friends and family.
<b>Feedback and monitoring</b>			
11. Self-monitoring behaviour	Establish a method for the person to monitor and record the behaviour as part of a behaviour change strategy.	Pedometer, intervention booklet & walking diary	Patients were asked to keep a daily record of the number of steps taken alongside the intensity and duration of their walking
<b>Repetition and substitution</b>			
29. Graded tasks	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behaviour is performed.	Intervention booklet & walking diary	Patients were encouraged to set weekly goals and to gradually increase the number of steps taken week by week. They were asked to challenge themselves with each week but also set realistic/achievable goals whilst taking their chemotherapy schedules into consideration.
<b>Goals and planning</b>			
61. Goal setting (behaviour)	Set or agree to set a goal defined in terms of the behaviour to be achieved.	Walking diary	Patients were asked to set specific weekly step count goals stating when and how many steps they intend to take
65. Action planning	Prompt detailed planning of performance of the behaviour (must include at least one of context, frequency, duration and intensity). Context may be environmental (physical or social) or internal (physical, emotional or cognitive).	Walking diary	Patients were encouraged to set weekly plans outlining the amount of walking they intend to do each day of the week. Action plans included the duration, intensity, day of the week and time of day they aim to complete their walking.
<b>Comparison of outcomes</b>			
72. Persuasive source	Present verbal or visual communication from a credible source in favour of or against the behaviour.	Intervention booklet & verbally	Each patient was presented with an intervention booklet stating the benefits of walking which were adapted from credible sources. The patients' consultant also verbally recommended and encouraged patients to participate in the physical activity involved in the study.

## Procedure

The researcher will recruit participants, collect cognitive and psychosocial data at pre and post-intervention and facilitate the delivery of the physical activity intervention. Initially, consenting participants will be asked by the researcher to complete a self-report cognitive functioning questionnaire, a battery of objective tests of cognitive impairment and a questionnaire pack assessing quality of life and emotional well-being pre-chemotherapy to allow familiarisation with the researcher and research materials. They will be asked to wear ActiGraph GT3X+ accelerometers for 10 hours a day for 7 days for a measure of habitual walking after the familiarisation assessment [63]. These data will be collected prior to receiving chemotherapy.

After completing two cycles of chemotherapy, participants will be asked to complete the same measures again at the clinic. Patients will then be randomised to either the intervention or control group following the

procedures outlined above. The walking intervention starts after 2 cycles of treatment in line with recommendations from oncologists who suggests that the intervention will be better received by patients after they have had 2 cycles of chemotherapy and understand what they are facing with regard to treatment side effects. The intervention group will be asked to commit to the 12 week walking intervention and will be provided with a booklet outlining the amount of walking they should take part in alongside guidance and tips on how to incorporate this into their daily routines. The intervention group will also be asked to commit to a minimum of 150 minutes of moderate intensity walking per week for the duration of the 12 week intervention, in line with recommended guidelines [61]. They will be told how to monitor their own intensity levels and will be encouraged to aim to walk at moderate levels of intensity for 150 minutes a week for the duration of the intervention. Walking schedules will be self-prescribed

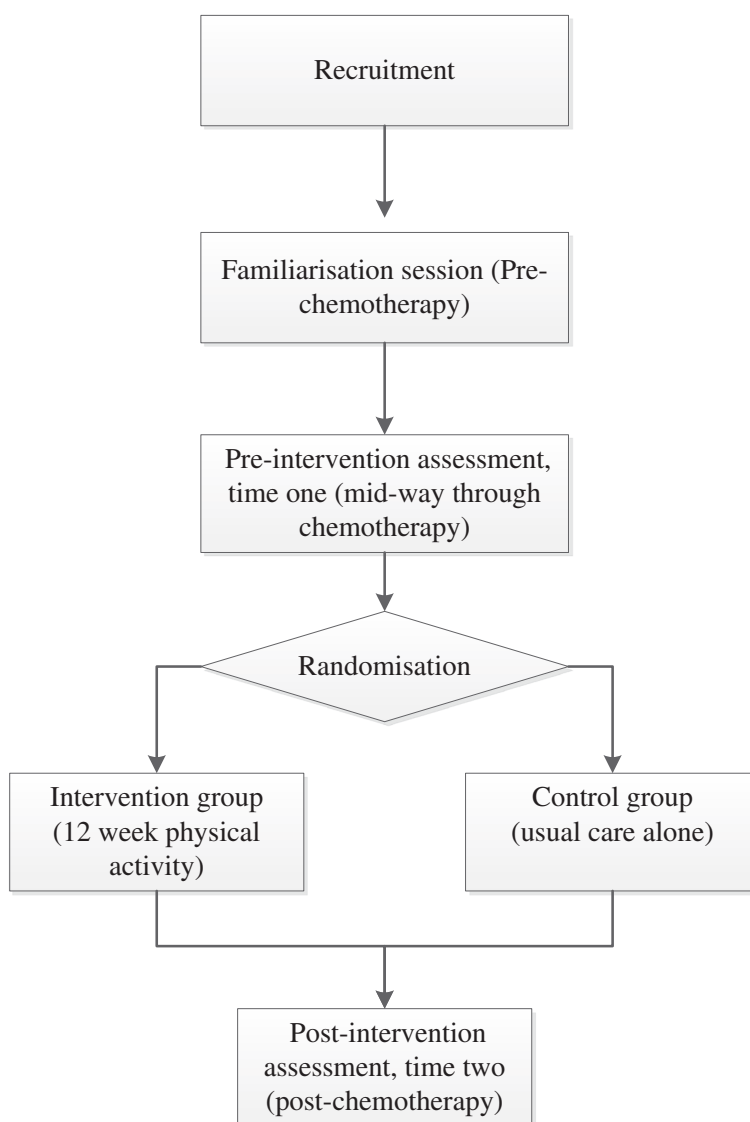
by participants but the researcher will recommend that they begin by completing 10 minutes of walking at any one time and then steadily increase the duration of walking to 30 minutes. Participants will be provided with a pedometer for the duration of the intervention and will be asked to log their walking for the 12 week period. Those randomised to the control group will continue to receive usual care alone.

Post-intervention (after the completion of 6 cycles of chemotherapy), all participants will be asked to wear the accelerometer for a further 10 hours a day for 7 days. In addition, they will be asked to complete the same questionnaires and neuropsychological tests as those completed at pre-chemotherapy and mid way through chemotherapy. At the end of the study the control group

will receive the intervention booklet (see Figure 1 for flow chart of study methods).

#### Measures of physical activity

Accelerometers (motion sensors which detect accelerations produced by the human body), will be worn by all participants for 10 hours a day for 7 days at baseline and post-intervention to assess habitual physical activity [63]. Pedometers will be worn by participants randomised to the intervention group for 10 hours a day for the duration of the twelve week intervention in order to record frequency of steps taken. They will also complete the Borg Rating of Perceived Exertion Scale [64] and The Talk Test [65] to subjectively monitor the intensity of their walking during the intervention.



**Figure 1** Flow diagram illustrating study methods.



### Outcome measures

All outcome measures will be completed at three time points: baseline (familiarisation), mid way through chemotherapy (pre-intervention) and after the completion of chemotherapy (post-intervention). All outcome measures have been validated in this population.

### Objective measures of cognitive functioning

The Stroop test [66] will be used to measure executive function. Working memory will be tested using forwards and backwards digit span as used in the Wechsler Adult Intelligence Scale-III [67]. Sustained attention will be measured using a computerised version of the Sustained Attention to Response Task [68]. Visuospatial skills will be measured using the WAIS Block Design subset as used in the Wechsler Adult Intelligence Scale-III [67].

### Subjective measure of cognitive functioning

The Cognitive Failures Questionnaire [69] is a 25 item questionnaire which will be used to assess the primary outcome measure of perceived cognitive function. The questionnaire will ask participants to reflect on minor mistakes made across a one month time frame. Responses are measured on a five-point Likert scale ranging from 'very often' to 'never'.

### Subjective measures of emotional wellbeing

Anxiety and depression will be measured using the 14 items Hospital Anxiety and Depression Scale [70]. Fatigue will be measured using The Functional Assessment of Cancer therapy-Fatigue [71]. Self esteem will be measured using the Self-Esteem Scale [72]. The rating scale requires participants to indicate how they feel in relation to a series of 10 statements. Emotional Distress will be measured using the shortened version of Profile of Mood States [73]. Participants will first be asked to complete questions regarding their anxiety and depression, followed by self-esteem, fatigue, perceived cognitive function and lastly mood.

### Additional information collected at baseline

Demographic and cancer diagnosis data will be collected from all participants at baseline. Participants will be asked to state the average number of hours they spend exercising in an average week before involvement in the study using the General Practitioner's Activity Questionnaire.

### Sample size

Sample size for the study was calculated based upon previously published data [37,38] and Cohen's Power Primer [74]. According to a prospective calculation, for a repeated measures ANOVA, 26 participants per group are required to detect a large effect size with power of 0.80

and  $\alpha$  set at .05. It is reasonable to assume a large effect size in this population based upon previous research [37,38] and their memory performance on the digit span. Allowing for 20% attrition due to withdrawal and illness we aim to recruit 31 patients per group.

### Statistical analyses

Quantitative data will be entered into Statistical Package for the Social Sciences (SPSS) and intention to treat analysis will be used in line with the CONSORT statement. To test the effectiveness of the physical activity intervention on cognitive function, a series 2x2 mixed ANCOVAs will be carried out controlling for age and menopausal status (controlling for natural differences in cognitive function associated with age and menopausal status). Participant group (intervention or control) will be entered as the between subjects factor and time (pre-intervention and post-intervention) will be entered as the within subjects factor. In addition, to test the effectiveness of the intervention on quality of life and measures of well-being another series of 2x2 mixed measures ANOVA will be carried out between the intervention group and control group. Post-hoc analysis will be carried out using a series of t-tests to check for differences between the intervention and control group. Lastly, to test whether emotional distress mediates between amount of physical activity (duration of walking and steps taken) and self-report cognitive functioning for the intervention group, a series of mediation analyses will be carried out using regression analyses.

### Ethics

Written informed consent will be gained by all patients and GPs will be informed of their participation within the study. The study has been granted ethical approval by the National Health Service, local ethics board for the Leicester Royal Infirmary and by Loughborough University's ethics committee.

### Discussion

Cognitive difficulties associated with chemotherapy in adjuvant and neo-adjuvant breast cancer patients have been well established in research but rarely addressed through the implementation of interventions. As the number of breast cancer survivors increases each year research has become more focused upon developing effective interventions to aid transition back to everyday functioning (post-treatment). This intervention has been developed with the aim of managing cognitive difficulties following treatment which often affect patients for years after completion. Cognitive difficulties experienced by patients following the completion of treatment have been reported to challenge their abilities to return to work, in turn lowering levels of self-esteem further.

The outcomes of this intervention will add valuable insight into treatment for cognitive difficulties experienced by breast cancer patients as a result of chemotherapy which is an essential element of their treatment. Findings will provide healthcare professionals with guidance for additional care both during and after the completion of treatment and help improve current services. It will also help direct future research to improve the ongoing well-being of breast cancer survivors.

#### Competing interests

The study is funded by Loughborough University as part of a PhD project. The authors declare that they have no competing interests.

#### Authors' contributions

KG, FM and DW contributed to the conception and design of the study as well as writing and editing the manuscript. SA, IB and KK are contributing to the acquisition of data through the Leicester Royal Infirmary Hospital. All authors read and approved the final manuscript.

#### Acknowledgements

We would like to thank all participants who have agreed to take part in the clinical trial and have given us their time and input into the study. This activity was conducted under the auspices of the National Centre for Sport and Exercise Medicine (NCSEM) England, a collaboration between several universities, NHS trusts and sporting and public bodies. The views expressed are those of the authors and not necessarily those of NCSEM England or the partners involved.

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Received: 20 October 2013 Accepted: 16 April 2015

Published online: 23 April 2015

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