Feasibility and Acceptability of a Computerized Working Memory Training in Breast Cancer Survivors

Sheryl Wyant

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

University of Washington

2017

Reading Committee:

Ardith Doorenbos, Chair

Margaret Heitkemper

Diana Buchanan

Kathleen Shannon Dorcy

Program Authorized to Offer Degree

School of Nursing

University of Washington

Abstract

Feasibility and Acceptability of Computerized Working Memory Training in Breast Cancer Survivors

Sheryl Wyant

Chair of the Supervisory Committee:
Ardith Doorenbos, PhD, RN, FAAN
School of Nursing
Biobehavioral Nursing and Health Informatics

Purpose: To evaluate the feasibility and acceptability of an in-home, computerized, working memory training program for breast cancer survivors.

Design: A randomized wait-list control trial.

Setting: Breast oncology clinic at a comprehensive cancer center.

Sample: Female breast cancer survivors (n=15), aged 43-64, who self-reported persistent cognitive deficits and were 18 months to five years post primary oncologic treatment(s).

Methods: Eligible participants completed baseline measures and then were randomized to a wait list control (n=7) or immediate intervention group (n=8). The intervention was a computerized working memory training protocol for six weeks (5 days a week and up to 35 minutes a day) and included a weekly coach phone call to review training progress. Baseline (T1) and post measures (T2) included five PROMIS® short form measures (depression, anxiety, fatigue, applied cognition general concerns, and applied cognition executive function), Functional Assessment of Cancer Therapy Cognition Version 3 measure, and seven neuropsychological tests (Rey Auditory Verbal Learning Test; Wechsler Adult Intelligence Scale IV Symbol Search and Coding and Letter Number Sequencing; Trails A and Trails B tests; and Delis-Kaplan Executive Function Color Block test). Wait list control participants were offered

the working memory computerized training program after completing T2 measures. An acceptability survey was completed by all participants who participated in the training program.

Main Research Variables: Feasibility measures: recruitment, attrition, number of weekly coach phone calls achieved, and reasons individuals declined to participate in the study. Acceptability measures: adherence to the training schedule (five days a week, for six weeks), number of participants who completed >24 training blocks in six weeks, participant satisfaction, ease of use, comprehensibility of training directions, and recommendation to other breast cancer survivors experiencing cognitive deficits. Trends in difference scores (posttest scores adjusted by baseline scores) were analyzed for neuropsychological tests, PROMIS® short form measures, FACT-Cog measure, and working memory training index score.

Findings: Twenty-seven eligible survivors were referred to the study,15 were enrolled (56% recruitment rate), and two wait list control participants (87% retention rate) withdrew at T2. Thirteen participants completed T1 measures, T2 measures, and computerized working memory training (at least 24/30 training sessions). All weekly coach calls were achieved. The acceptability measures were rated positively with high values. The difference scores were analyzed using the Mann- Whitney U test. Statistically significant results included two PROMIS® measures: applied cognition general concerns U (n_{II}= 8, n_{WLC}=5) =5.0, Z = -2.196, p_{exact}=.030; applied cognition executive function U (n_{II}= 8, n_{WLC}=5) = 4.0, Z = -2.34, p_{exact}=.019; and three FACT Cog subscales: Perceived Cognitive Impairments U (n_{II} =8, n_{WLC}= 5) = 5.0, Z = - 2.02, p_{exact}= .030, Impact of Perceived Cognitive Impairments on Quality of Life U(n_{II} = 8, n_{WLC}=5)) = 4.5, Z = -2.291 , p_{exact}= .022, and Perceived Cognitive Abilities U(n_{II} = 8, n_{WLC} = 5) = 3.5 , Z = -2.422 , p_{exact}= .011. The results demonstrate that the immediate intervention group reported a greater decrease in cognitive impairment symptoms compared to the wait list control group for these measures.

Conclusions: The in-home computerized working memory intervention was feasible, acceptable, and safe. There was a trend in some of the difference scores demonstrating improvements in cognitive performance for the immediate intervention group after the working memory training.

Implications: This study aimed to address the gap in evidence-based treatments available for breast cancer survivors who report persistent cognitive deficits. This research extended a working memory intervention with demonstrated efficacy in other populations to breast cancer survivors and tested a

scalable, practical, intervention. The findings support the need for a larger randomized control study to evaluate efficacy of this intervention.

Table of Contents

List of Figures

List of Tables

A Computerized Working Memory Training Program for Breast Cancer Survivors: Study Design and Protocol

1. Introduction

Advances in breast cancer diagnosis and treatments have resulted in an estimated 3. 5 million breast cancer survivors in the United States today. (American Cancer Society, 2016) Many of these survivors experience late effects and persistent symptoms related to cancer and cancer treatments. Since the 1990' s there has been a growing body of science describing cognitive impairments in a subset of breast cancer survivors. Wefel et al. reported that breast cancer survivors who experience persistent cognitive impairment do not show significant improvement over time and may in fact develop additional cognitive impairments.(Wefel, Saleeba, Buzdar, & Meyers, 2010) These cognitive impairments are described as a sequence in which individuals experience the most impairments in the first six months after oncologic treatment(s) followed by some improvement or stabilization at one to two years.(Correa & Ahles, 2008) Cognitive impairment is one of the most troubling persistent symptoms reported by up to 60% of breast cancer survivors. (Chen et al., 2013)

The severity of cognitive impairments in this subset of cancer survivors is reported as mild to moderate, one and a half to two standard deviations below the adult normative means.(Wefel, Kesler, Noll, & Schagen, 2015) These milder impairments, however, are associated with a significant negative impact on interpersonal relationships, the ability to learn, self-confidence, and level of chronic distress.(Boykoff, Moieni, & Subramanian, 2009; Cull et al., 1996; Jansen, Cooper, Dodd, & Miaskowski, 2011; Myers, 2012, 2013) These impacts may in turn diminish the level of one's independent function and quality of life.(Jansen et al., 2011; Myers, 2012, 2013)

Several longitudinal studies of breast cancer survivors have identified objective cognitive impairments in working memory as compared to age-matched healthy control and cancer control groups.(Ahles et al., 2010; Jansen et al., 2011; Noal et al., 2011; Quesnel, Savard, & Ivers, 2009) Working memory is an active multicomponent cognitive system which temporarily stores and manipulates necessary information for a variety of cognitive tasks (e.g. learning, problem solving, reading comprehension, reasoning, and

visual spatial processing to navigate tasks).(Cherrier et al., 2013; de Ruiter et al., 2011) There is evidence that computerized training has efficacy in the improvement of working memory in non-oncology clinical populations.(de Ruiter et al., 2011; Dunning, Holmes, & Gathercole, 2013; Klingberg et al., 2005)

The conceptual definition for working memory for this research study is working memory is a cognitive system that includes verbal working memory (VWM), visual spatial working memory (VSWM), executive function (EF). VWM refers to the ability to remember words or a story.(de Ruiter et al., 2011) VSWM refers to the ability to understand and conceptualize visual representations and spatial relationships when performing a task.(de Ruiter et al., 2011) EF is defined as a type of supervisory attentional control that selects strategies and integrates information from different sources.(de Ruiter et al., 2011) EF is necessary for goal directed behaviors such as planning and initiating actions (getting started); monitoring and changing behaviors as needed; and anticipating and planning for the future when faced with novel tasks and situations.(de Ruiter et al., 2011; S. Kesler et al., 2013; S. R. Kesler, Kent, & O'Hara, 2011)

Research on computerized interventions to treat persistent cognitive impairments in breast cancer survivors is limited but ongoing.(Barton et al., 2011; Chen et al., 2013; S. Kesler et al., 2013; Von Ah et al., 2012) The working memory system has not been targeted for cognitive intervention and no studies were identified in the literature that have established the feasibility and acceptability of a computerized working memory intervention, Cogmed^{QM}, in breast cancer survivors.

2. Aims

This study used an existing intervention, which has been found to be successful in the treatment of working memory impairment in adults diagnosed with schizophrenia, ADHD, alcohol disorders, elderly, and children treated with radiation for brain cancer. This research extended a proven working memory intervention to breast cancer survivors. The study will provide preliminary evidence for future efficacy investigation of a scalable, practical working memory intervention. The purpose of this study was to evaluate the feasibility and acceptability of an in home, computerized, working memory training program for breast cancer survivors.

The specific objectives were to:

1. To assess the feasibility and acceptability of the in-home 6 -week computerized working memory training program.

    1a: Evaluate feasibility of study procedures (recruitment, attrition rate and reason, weekly phone calls completed with participants, and reason declined to participate)

    1b: Evaluate the acceptability of an adaptive computerized working memory training intervention (adherence to training schedule, training completion, and participant satisfaction with computerized training, ease of use, comprehensibility of program instructions, and likelihood to recommend the program to other breast cancer survivors).

2. Evaluate the difference in the posttest means at T2 (Week#7) adjusted for T1 (Baselines) for neuropsychological tests (Rey Auditory Verbal Learning Test, WAIS IV symbol test, WAIS IV coding test, Delis Kaplin Executive Function word color tests, Trails A and Trails B tests, and WAIS IV Letter and Number sequencing test); self-report Patient-Reported Outcomes Measurement Information System, PROMIS, short form surveys (Depression, Fatigue, Anxiety, Applied Cognition General Concerns, Applied Cognition Executive Function Short Form), and the Functional Assessment of Cancer Therapy Cognition (Version 3) (FACT-Cog) survey between the intervention group and wait control group.

3. Methods

3.1 *Study Design and Setting*

The study is a wait list control, randomized controlled trial that was implemented at a breast health clinic in a comprehensive cancer center.

3.2 *Ethical Approval*

The research study protocol received the full institutional review board approval (IRB).

3.3 *Pre-Screening*

A partial waiver of consent and HIPAA waiver were granted by the IRB for the sole purpose of determining potential participant eligibility prior to initial contact for recruitment. The principle investigator accessed provider clinic patient lists and reviewed medical records (n=693) to identify potential

participants' who were medically eligibility for this study (n=27). A list of potential participants was provided to the oncology provider prior to each clinic for review. At the clinic appointment, eligible participants were asked by their oncologist if they were experiencing persistent cognitive impairments. Individuals with persistent cognitive impairments (n=27) were referred to the principle investigator who was available to meet with them immediately in the clinic and share information about the study. Twelve potential participants declined to participate in the study. The reasons for declining to participate in the study were: no access to a computer (n=1) and travel time and costs associated with the study requirement for two in-person study appointments (n = 11).

3.4 *Eligibility, Recruitment*

Participants eligibility requirements included a diagnosis with stage 0,1,2, or 3 breast cancers, at least > 18 years old, 18 months to five years post oncologic therapy (e.g. surgery and chemotherapy and/or radiation), experiencing persistent cognitive impairments, and a score >19 on the mini mental state exam. In addition, participants needed access to a computer with speakers/audio and a mouse; to agree to return for in person baseline and post study measures; and to have the ability to read, write, and speak English. Exclusion criteria included a history of more than one malignancy; central nervous system surgery, radiation, or disease (e.g. stroke, Parkinson's); psychiatric disorders; learning disabilities; and any uncorrected sensory impairments.

Potential participants were provided a one page study information document and a form with inclusion and exclusion criteria for review. Once individuals confirmed their interest in the study, copies of the research consent forms and the study schedules for both the immediate intervention group and the wait list control group were reviewed and questions were answered. The study schedules listed the all the required study measures, computerized training requirements, weekly coach calls, approximate time to complete each requirement, and timing for each of the requirements (See Table 1 and Table 2). The research study phone number and email were provided for individuals to schedule their consent signing and baseline measures appointment.

3.5 *Sample*

Fifteen breast cancer survivors who self-reported persistent cognitive impairments were recruited over five and one-half months. Eligible participants each received payment of a $50.00 cash card after baseline measures were completed and an additional $50.00 cash card following completion of the post measures at week #7- #8. The payment was provided to help defray costs associated with travel and parking to attend the two in-person sessions required to complete study measures.

3.6 *Intervention*

The adult Cogmed[QM] Version 4.0 computerized working memory training program (NCS Pearson Inc., Upper Saddle River, NJ) was the intervention used in this study. The program is compatible with PC and MAC® computers. The program worked with the Internet Explorer, Firefox, and Google browsers.

A licensing agreement for the program was purchased which included individual registrations to be used within a 12-month time span. The license included an online Cogmed coach training program which consisted of six modules and a coach resource site with coaching manuals and quality assurance guides. The principle investigator, PI, successfully completed the required coach training to enable her to serve as a coach to the individuals participating in the training. Technologic support was also available to the coach by email and phone for assistance with any problems related to screen or program functional issues or internet and server connection issues that study participants might have experienced.

The computerized training program required that participants were regularly monitored and received weekly coach phone calls. In this study, each participant's training progress was reviewed on line prior to the coach call using a standardized review template. The template included ten important factors to evaluate participant training performance. Some of the factors evaluated weekly were the number of training blocks completed in the past week, the pattern of the training performance (e.g. even or uneven), the time of day training was completed and its relationship to training performance, training level achieved, and change in the computed training index level (e.g. a trend of improvement or decline).

Cogmed[QM] has a total of eleven possible working memory training exercises. Each training session is referred to as a "block".(Pearson, 2014) A block consisted of three to eight different types of working memory training exercises, each with multiple trials. The program is an adaptive training

program; it becomes more difficult or less difficult depending on the participant's responses during each trial for each type of working memory exercises.

There are different working memory intensity protocols available to select. The original Cogmed[QM] was developed and tested as a five week, 50 minutes a day program. Some patient populations experiencing persistent fatigue had difficulty completing the intense standard treatment dose training program.(Lundqvist, Grundstrom, Samuelsson, & Ronnberg, 2010) Cogmed offers variable dose training programs to accommodate patients with fatigue. Breast cancer survivors frequently report fatigue, therefore the protocol selected for use in this study was the six weeks, 35 minutes a day, five days a week (total 30 blocks).

Participants randomized to the immediate intervention group were registered on line and received a unique number letter password and code from Cogmed that included no personal identifiers. The on-line registration requires only the participant's month of birth, year of birth, and gender. Participants in the immediate intervention group completed the on-line registration; practiced signing into the training site and completed several of the working memory exercises on the computer with a mouse; and reviewed the training schedule with the investigator at baseline (T1).

When participants logged into the Cogmed[QM] training program for the first time, they were asked to complete a three-part questionnaire with a total of 26 questions. The participants had the option of selecting a response of "prefer not to answer" for each of the 26 questions. Participants were asked about their perceptions of attention abilities compared to others their age (15 questions) and the degree to which they agree with statements about motivation related to the working memory training (10 questions). An anchored visual analog scale slider bar was used for participants to respond to questions 1-25. The questionnaire also asked participants to select three behaviors from a checklist of 16 functional behaviors related to working memory (e.g. problem solving, staying focused, remembering) that they would like to experience improvement.

This same questionnaire was repeated at the end of the training program in Block #30 and summarized in a progress report. The summary report included the percent of change for attention, motivation, and functional behavior improvements. It also included chart using a visual scale with a directional arrow indicating the positive or negative change from baseline for each of the questions.

The computerized training was completed in the participant's home. Participants linked via the internet directly to the training site. The participants received a weekly coach phone call to review training progress, answer questions, and assess and troubleshoot any on-line training access or technological difficulties. All participants were provided the Cogmed^{QM} training at no cost.

3.7 Measures

3.71 *REDcap*^{TM} *web tool*

The web-based data collection platform, REDcap^{TM}, was utilized in the design, build, and customization of study surveys used for this research study. REDcap^{TM} allowed for the direct download of PROMIS symptom surveys in a web format into the REDcap™ Online Designer and the use of an auto-scoring feature. This web research tool was easily accessed at all the research sites by the investigator and there were no technological difficulties experienced with the tool during the study.

3.71 Feasibility Measures

Feasibility measures included recruitment, attrition, weekly coach calls achieved, and the reason potential participants declined to participate in the study. Feasibility data were tracked in a weekly database report for both individual participants and as aggregated data.

3.72 Acceptability Measures

Acceptability measures included adherence to the training program; training completion; and acceptability survey responses. Adherence to the training program was evaluated by the number of working memory training blocks completed each week. Training completion is defined by Cogmed as finishing 24 of 30 assigned training blocks. (de Ruiter et al., 2011)

The acceptability survey on REDcap™ asked five questions. An anchored visual analog scale (VAS) with a slider bar feature was used for responses to questions about ease of use and comprehensibility of the training exercises directions. The result of the VAS slider bar scales was a number between 0 and 100 in the REDcap™ data base. A five point Likert scale was used to rate overall satisfaction with the training program. A four point Likert scale was used to rate if the participant would recommend the training program to other breast cancer survivors with persistent cognitive deficits. The survey also included an open-ended question asking what changes, if any, participants noticed about

their memory following the completion of the computerized cognitive working memory program. The participants had an unlimited space to comment their response to this question.

The acceptability survey was completed on the REDCap™ system during the in-person post measure visit (T2) by the immediate intervention group. The wait-list control group members who elected to participate in the computerized working memory training after completing post measures were emailed the acceptability survey link via REDcap™ after completion of the six weeks of training (T3).

3.73 Self Report outcome measures

3.73.1 PROMIS Measures

Five Patient Reported Outcomes Measurement Information System (PROMIS) symptom short form surveys (8 questions) were administered at baseline and at Week #7-8. The PROMIS surveys included Anxiety Short Form (α= 0.97),(Avis, Ip, & Foley, 2006) Depression Short Form (α= 0.98),(Bowers, Waddell, & McCarthy, 2010) Fatigue Short Form (α= 0.99),(Avis et al., 2006) Applied Cognition General Concerns Short Form (α= 0.98),(Buwalda & Schagen, 2013) and Applied Cognition Executive Function Short Form (α= 0.98).(Buwalda & Schagen, 2013) The symptoms of anxiety, depression, and fatigue were included in this study as they have been strongly correlated with the self-report of perceived cognitive deficits as well as working memory neuropsychological tests in cancer survivors.(Ganz et al., 2013; Jenkins et al., 2006; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; van Dam et al., 1998)

All PROMIS measures are scored using the final re-centered item response theory (IRT) item parameters and transformed to a T-score metric (mean=50, SD=10). The study PROMIS measures were scored using the HealthMeasures Scoring Service at the web site https://www.assessmentcenter.net. This scoring service uses item level calibrations, looking at the response for each item for each participant, which provides a more accurate score compared to manually adding up raw scores and comparing the scores to a table. The higher the PROMIS T-score, the higher or worse levels of the symptom is being measured.

3.73.2 FACT Cognitive Function

The FACT Cognitive Function Version 3 (α= 0.71 – 0.93)(Avis et al., 2005) is a self-report survey to assess cognitive function in cancer patients and consists of 4 subscales (Perceived Cognitive

Impairments, Comments from Others, Perceived Cognitive Abilities, and Impact on Quality of Life). All 37 questions included in the survey ask the participant to indicate the frequency in which each cognitive function has occurred in the last seven days.(Buwalda & Schagen, 2013) Each subscale is manually scored using a subscale formula on the scoring guideline template (http://www.facit.org/FACITOrg). The perceived cognitive impairments subscale score range is 0-72. This subscale includes all negatively worded items that are reverse scored. The result is that the higher scores on this subscale represent better cognitive function. The comments from others subscale score range is 0-16. The perceived cognitive abilities subscale score range is 0-28. The impact of quality of life subscale score range is 0-16 (FACIT http://www.facit.org/FACITOrg/Questionnaires). The Perceived Cognitive Impairment subscale is recommended as the primary score to be reported.(de Ruiter & Schagen, 2013)

3.8 *Objective Outcome Measures – Neuropsychological Memory Tests*

Seven memory neuropsychological tests were administered to participants using paper and pencil at T1 and T2. All five tests have moderate to high reliability reported.(Attal et al., 2014; Carter, 2006)·(Arpels, 1996; Carpenter, 2001) (Attal et al., 2014) These tests were recommended by a neuropsychologist to objectively measure working memory at baseline and Week #7-8. It is important to note, that the neuropsychological tests utilized were distinctly different from the Cogmed^{QM} exercises that the study participants trained on. Thus, participants were not trained to the neuropsychological tests utilized to evaluate cognitive performance at T1 and T2. While different versions of the tests exist, the same version for each test was used at baseline and Week # 7 -8. One purpose of the wait list control group study design was to provide a measure of practice (learning) effects since the study protocol used a repeated measure of the five neuropsychological tests within a relatively short time span of seven to eight weeks.

The Rey Auditory Verbal Learning Test, RAVLT, is a recall and recognition test that assesses immediate memory span, new learning, and recognition memory.(Carpenter, 2001) Symbol recognition and coding are timed tests of processing speed and visual attention.(Carpenter, 2001) D-KEFS color word tests include four timed tests used to assess the ability to inhibit an overlearned response and cognitive flexibility or one's executive function.(Carpenter, 2001) Trail Making Tests A and B are two timed tests of attention, speed, and mental flexibility.(Attal et al., 2014) The Letter-Number Sequencing

Test assesses working memory, mental manipulation, attention, concentration and short term auditory memory.(Carter, 2006)

Each of these tests were manually scored by a neuropsychology psychometrist and then independently scored by the principle investigator as an independent double check of the results. The RAVLT test uses gender and age as factors in the scoring. The Symbol Recognition, Coding, and Letter Number Sequencing tests use the single factor of age. The Trails A, Trails B, and the DKEF color word tests use gender, age, and years of education as factors in the scoring. These tests are scored (raw score), followed by a scaled score and then the scaled score is compared to the normative tables for percentiles. These neuropsychological tests have not been normed in adult breast cancer population.

3.9 *Randomization*

Randomization was the final step in the study baseline appointment after all self-report questionnaires and neuropsychological tests were completed. There were possible implications related to accrual if potential participants were randomized prior to completion of all baseline questionnaires and tests. An electronic randomization program was used to generate randomization codes after entering the participant's age, PROMIS depression T- score, and years of education level achieved. The algorithm used for randomization was a modification of the minimization method based on an overall imbalance score that measured how far out of balance the study was based on given set of random assignments.(Pocock, 1983) When a new study participant was ready for randomization, the algorithm computed what the imbalance score would be if the participant were assigned to group A or what it would be if the participant were assigned to group B. Next an unequal randomization was completed which had a high probability of assigning the participant to the group which resulted in the least imbalance and a low probability of assigning the participant to the group resulting in the greatest imbalance. Participants were randomized to the immediate intervention or the wait-list control group and informed following the baseline assessment of their group assignment.

3.10 Study Flow

Progression through the study is outlined in Figure 1.

3.11 *Dropout from the study*

Participants who wished to drop from the study at any time after joining were asked for the reason they were dropping out. The reasons participants drop out of a study is key to inform the design of future efficacy trials. All participant data collected prior to dropping from the study (n=2) remained in the study records and was included in the analysis of the baseline results.

3.12 Analysis

The analysis was performed with descriptive statistics. No *a priori* power nor sample size calculations were performed as this was a feasibility, acceptability study and efficacy was not an aim of this study. The baseline data for all participants in this study were used and the data from 13 participants were used to evaluate the difference between posttest means adjusted for baseline means.

4. Discussion

4.1 *Intervention strengths and weaknesses*

The Cogmed^{QM} has a body of research and randomized control trials that suggests objective improvements both immediately after training as well as one year post training in non-oncology populations.(Dunning et al., 2013; Shipstead, Hicks, & Engle, 2012) For this pilot study the strengths of on-line computerized working memory intervention included: 1) both verbal working memory and visual spatial working memory were trained by the program; 2) an adaptive algorithm was utilized which supported that the training was being carried out at a challenging level and stretched the limit of working memory capacity; 3) each training block included graphed results of each working memory exercise and 4) a summary training report was available at the end of the training to review with study participants that included the change in training index score and the percentage change in behavioral goals, attention, and motivation which were assessed before and after the training.

One significant limitation of this type of computerized cognitive training program was that it is difficult to know which of any of the training exercises contributed to cognitive improvements and to identify which specific mechanisms of the working memory system are improved.(Bennett, Bagnall, & Jose Closs, 2009)

Another limitation of this program was the purchase of the Cogmed^{QM} license that was available for schools which made the extraction of each participant's trial data results for each training exercise

extremely time intensive. The individual trial data for each training exercise for each training block was extracted to evaluate the dose fidelity of the intervention.

4.2 Methodological strengths and weaknesses

The methodological strengths of this study include:

1) the eligibility requirement of at least 18 months post oncologic therapy helped to minimize the maturation effects of continued cognitive improvement during the first 18 months' post treatment,

2) the use of a computerized randomization algorithm to balance the immediate intervention and wait list control groups using factors that affect cognitive performance including age, years of education, and depression T-scores,

3) the use of a wait list control study design to provide an assessment of neuropsychological test practice effects

4) the opportunity for the wait list control group to participate in the computerized training program after the week 7-8 post measures.

For a larger efficacy trial, changes recommended in the study design and methods would include:

1) formation of a team to conduct the study that would allow for blinding the researcher who is performing the coach calls and the posttest measures to improve construct validity,

2) use of an attention control condition for the wait list control group,

3) improving the rigor of treatment adherence by having participants stop their training at the end of seven weeks,

4) provide participants with a treatment calendar schedule to help support the expectation of training 5 days a week for 6 weeks and

5) start all participants to train during week #1 on a Monday, which would help both the participant and the researcher to easily track the training expectation of 5 days a week.

5. *Conclusion*

This research was innovative in the utilization of computerized working memory training intervention, CogMed^{QM} as it expands the population targeted to breast cancer survivors. The data from

this feasibility study will help to inform a future randomized controlled trial to evaluate efficacy of the computerized training in breast cancer survivors. This intervention is both easily scalable and may be readily incorporated into clinical practice.

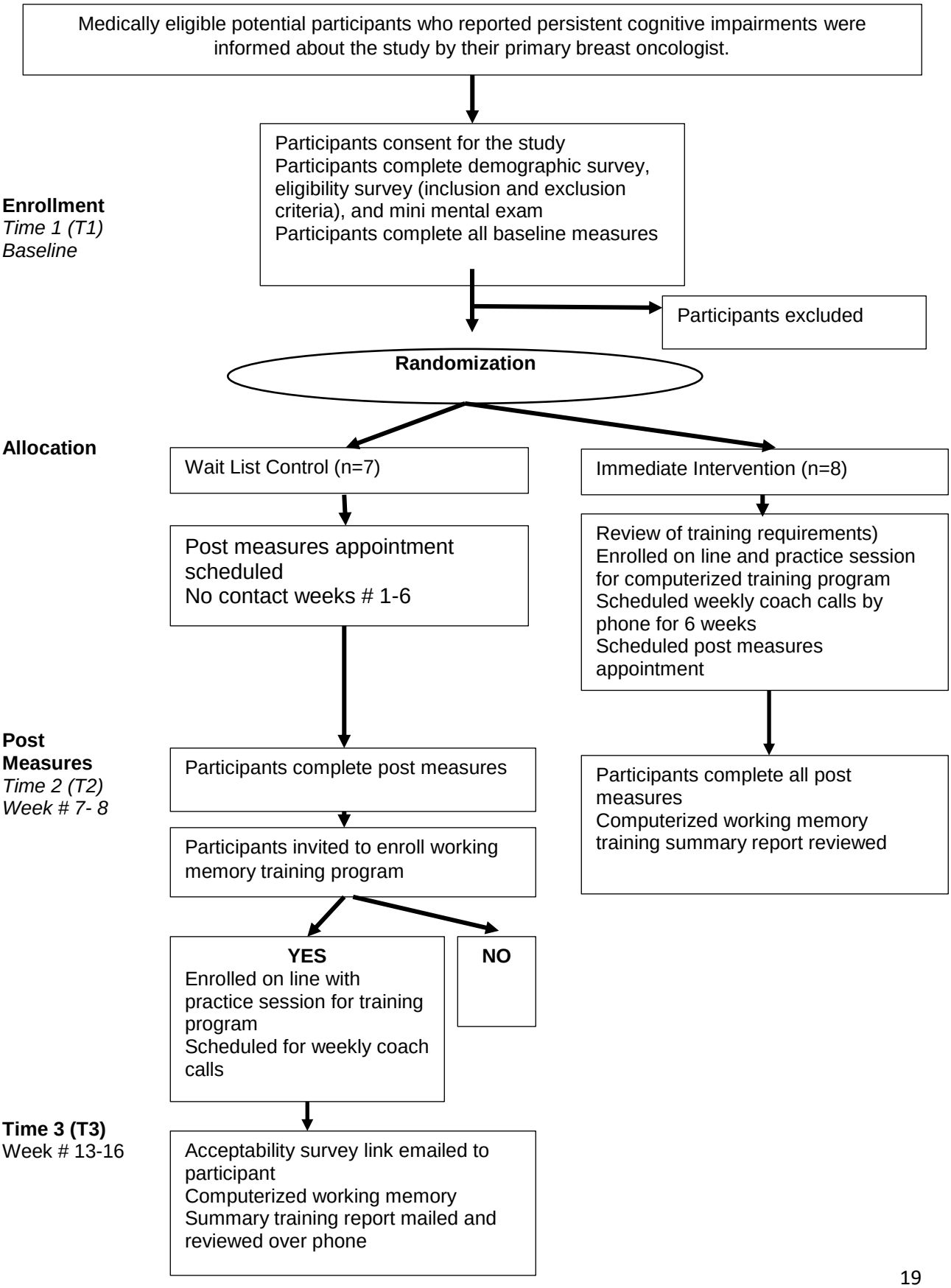
Table 1. Schedule of Participants in Immediate Intervention Group Study Requirements

Study Requirements	Time to Complete In minutes	Pre-Randomization	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7-8
Information consent	10	X							
HIPPA Consent	5	X							
Demographics Questionnaire – (14 questions)	5	X							
FACT Cognitive Function (24 questions)	5	X							X
Applied Cognition General Concerns Short Form (8 questions)	4	X							X
Applied Cognition Executive Function (8 questions)	4	X							X
Anxiety Short Form (8 questions)	1-2	X							X
Depression Short Form (8 questions)	1-3	X							X
Fatigue Short Form (8 questions)	1-3	X							X
Five Neuropsychological Memory Tests	48	X							X
Mini- Mental State Exam – (11 exercises)	5-10	X							
Eligibility Screening Questionnaire – (17 questions)	5	X							
Computerized Cognitive Training Program Start Up Session including registration, practice exercises, baseline questionnaire	20		X						
Computerized Cognitive Training 5 days a week, 35 minutes a day, 6 wks			X	X	X	X	X	X	
Weekly phone calls	5-10		X	X	X	X	X	X	
Acceptability Questionnaire **-** (5 questions)	5								X
Computerized Cognitive Training Wrap up Session (review of progress report)	5								X

Table 2. Schedule of Participants in Wait- List Group Study Requirements

Study Requirements	Time to Complete In minutes	Pre-Randomization	Wks 1 - 6	Wk 7 -8	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13-14
Information consent	10	X								
HIPPA Consent	5	X								
Demographics Questionnaire – 14 questions	5	X								
FACT Cognitive Function (24 questions)	5	X		X						
Applied Cognition General Concerns Short Form (8 questions)	4	X		X						
Applied Cognition Executive Function (8 questions)	4	X		X						
Anxiety Short Form (8 questions)	1-2	X		X						
Depression Short Form (8 questions)	1-3	X		X						
Fatigue Short Form (8 questions)	1-3	X		X						
Five Neuropsychological Memory Tests	48	X		X						
Mini Mental State Exam	5-10	X								
Eligibility Screening Questionnaire – 17 questions	5	X								
Computerized Cognitive Training Program Start Up Session including registration, practice exercises, baseline questionnaire	20			X						
Computerized Cognitive Training 5 days a week, 35 minutes a day, for 6 weeks				X	X	X	X	X	X	
Weekly phone calls	5-10			X	X	X	X	X	X	
Acceptability Questionnaire (5 questions)	5									X
Computerized Cognitive Training Wrap up Session (review of progress report and brief questionnaire)	5									X

Figure 1. Trial design progression



References:

Ahles, T. A., Saykin, A. J., McDonald, B. C., Li, Y., Furstenberg, C. T., Hanscom, B. S., . . . Kaufman, P. A. (2010). Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol, 28(29), 4434-4440. doi: 10.1200/jco.2009.27.0827

American Cancer Society (2016). Cancer Treatment & Survivorship Facts and Figures 2016-2017. Atlanta: American Cancer Society.

Arpels, J. C. (1996). The female brain hypoestrogenic continuum from the premenstrual syndrome to menopause. A hypothesis and review of supporting data. J Reprod Med, 41(9), 633-639.

Attal, N., Masselin-Dubois, A., Martinez, V., Jayr, C., Albi, A., Fermanian, J., . . . Baudic, S. (2014). Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. Brain, 137(Pt 3), 904-917. doi: 10.1093/brain/awt354

Avis, N. E., Ip, E., & Foley, K. L. (2006). Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for long-term cancer survivors in a sample of breast cancer survivors. Health Qual Life Outcomes, 4, 92. doi: 10.1186/1477-7525-4-92

Avis, N. E., Smith, K. W., McGraw, S., Smith, R. G., Petronis, V. M., & Carver, C. S. (2005). Assessing quality of life in adult cancer survivors (QLACS). Qual Life Res, 14(4), 1007-1023.

Barton, D. L., Atherton, P. J., Bauer, B. A., Moore, D. F., Jr., Mattar, B. I., Lavasseur, B. I., . . . Loprinzi, C. L. (2011). The use of Valeriana officinalis (Valerian) in improving sleep in patients who are undergoing treatment for cancer: a phase III randomized, placebo-controlled, double-blind study (NCCTG Trial, N01C5). J Support Oncol, 9(1), 24-31. doi: 10.1016/j.suponc.2010.12.008

Bennett, M. I., Bagnall, A. M., & Jose Closs, S. (2009). How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain, 143(3), 192-199. doi: 10.1016/j.pain.2009.01.016

Bowers, J. M., Waddell, J., & McCarthy, M. M. (2010). A developmental sex difference in hippocampal neurogenesis is mediated by endogenous oestradiol. Biol Sex Differ, 1(1), 8. doi: 10.1186/2042-6410-1-8

Boykoff, N., Moieni, M., & Subramanian, S. K. (2009). Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. J Cancer Surviv, 3(4), 223-232. doi: 10.1007/s11764-009-0098-x

Buwalda, B., & Schagen, S. B. (2013). Is basic research providing answers if adjuvant anti-estrogen treatment of breast cancer can induce cognitive impairment? Life Sci, 93(17), 581-588. doi: 10.1016/j.lfs.2012.12.012

Carpenter, J. S. (2001). The Hot Flash Related Daily Interference Scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. J Pain Symptom Manage, 22(6), 979-989.

Carter, P. A. (2006). A brief behavioral sleep intervention for family caregivers of persons with cancer. Cancer Nurs, 29(2), 95-103.

Chen, X., Zhu, C., Li, J., Qiu, L., Zhang, L., Yu, F., . . . Wang, K. (2013). Dissociation of decision making under ambiguity and decision making under risk in breast cancer patients receiving adjuvant chemotherapy: a neuropsychological study. Brain Res, 1533, 63-72. doi: 10.1016/j.brainres.2013.08.015

Cherrier, M. M., Anderson, K., David, D., Higano, C. S., Gray, H., Church, A., & Willis, S. L. (2013). A randomized trial of cognitive rehabilitation in cancer survivors. Life Sci, 93(17), 617-622. doi: 10.1016/j.lfs.2013.08.011

Correa, D. D., & Ahles, T. A. (2008). Neurocognitive changes in cancer survivors. Cancer J, 14(6), 396-400. doi: 10.1097/PPO.0b013e31818d8769

Cull, A., Hay, C., Love, S. B., Mackie, M., Smets, E., & Stewart, M. (1996). What do cancer patients mean when they complain of concentration and memory problems? Br J Cancer, 74(10), 1674-1679.

de Ruiter, M. B., Reneman, L., Boogerd, W., Veltman, D. J., van Dam, F. S., Nederveen, A. J., . . . Schagen, S. B. (2011). Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. Hum Brain Mapp, 32(8), 1206-1219. doi: 10.1002/hbm.21102

de Ruiter, M. B., & Schagen, S. B. (2013). Functional MRI studies in non-CNS cancers. Brain Imaging Behav, 7(4), 388-408. doi: 10.1007/s11682-013-9249-9

Dunning, D. L., Holmes, J., & Gathercole, S. E. (2013). Does working memory training lead to generalized improvements in children with low working memory? A randomized controlled trial. Dev Sci, 16(6), 915-925. doi: 10.1111/desc.12068

Ganz, P. A., Kwan, L., Castellon, S. A., Oppenheim, A., Bower, J. E., Silverman, D. H., . . . Belin, T. R. (2013). Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. J Natl Cancer Inst, 105(11), 791-801. doi: 10.1093/jnci/djt073

Jansen, C. E., Cooper, B. A., Dodd, M. J., & Miaskowski, C. A. (2011). A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. Support Care Cancer, 19(10), 1647-1656. doi: 10.1007/s00520-010-0997-4

Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., . . . Winstanley, J. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer, 94(6), 828-834. doi: 10.1038/sj.bjc.6603029

Kesler, S., Hadi Hosseini, S. M., Heckler, C., Janelsins, M., Palesh, O., Mustian, K., & Morrow, G. (2013). Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Cancer, 13(4), 299-306. doi: 10.1016/j.clbc.2013.02.004

Kesler, S. R., Kent, J. S., & O'Hara, R. (2011). Prefrontal cortex and executive function impairments in primary breast cancer. Arch Neurol, 68(11), 1447-1453. doi: 10.1001/archneurol.2011.245

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlström, K., . . . Westerberg, H. (2005). Computerized Training of Working Memory in Children With ADHD--A Randomized, Controlled Trial. Journal of the American Academy of Child & Adolescent Psychiatry, 44(2), 177-186. doi: 10.1097/00004583-200502000-00010

Lundqvist, A., Grundstrom, K., Samuelsson, K., & Ronnberg, J. (2010). Computerized training of working memory in a group of patients suffering from acquired brain injury. Brain Inj, 24(10), 1173-1183. doi: 10.3109/02699052.2010.498007

Myers, J. S. (2012). Chemotherapy-related cognitive impairment: the breast cancer experience. Oncol Nurs Forum, 39(1), E31-40. doi: 10.1188/12.onf.e31-e40

Myers, J. S. (2013). Cancer- and chemotherapy-related cognitive changes: the patient experience. Semin Oncol Nurs, 29(4), 300-307. doi: 10.1016/j.soncn.2013.08.010

Noal, S., Levy, C., Hardouin, A., Rieux, C., Heutte, N., Segura, C., . . . Joly, F. (2011). One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. Int J Radiat Oncol Biol Phys, 81(3), 795-803. doi: 10.1016/j.ijrobp.2010.06.037

Pearson. (2014). Research Coaching Manual P. Inc (Ed.) (pp. 1-93).

Pocock, S. J. (1983). Clinical Trials: A practical approach: John Wiley and Sons Ltd.

Quesnel, C., Savard, J., & Ivers, H. (2009). Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. Breast Cancer Res Treat, 116(1), 113-123. doi: 10.1007/s10549-008-0114-2

Shilling, V., Jenkins, V., Morris, R., Deutsch, G., & Bloomfield, D. (2005). The effects of adjuvant chemotherapy on cognition in women with breast cancer--preliminary results of an observational longitudinal study. Breast, 14(2), 142-150. doi: 10.1016/j.breast.2004.10.004

Shipstead, Z., Hicks, K. L., & Engle, R. W. (2012). Cogmed working memory training: Does the evidence support the claims? Journal of Applied Research in Memory and Cognition, 1(3), 185-193.

van Dam, F. S., Schagen, S. B., Muller, M. J., Boogerd, W., vd Wall, E., Droogleever Fortuyn, M. E., & Rodenhuis, S. (1998). Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst, 90(3), 210-218.

Von Ah, D., Carpenter, J. S., Saykin, A., Monahan, P., Wu, J., Yu, M., . . . Unverzagt, F. (2012). Advanced cognitive training for breast cancer survivors: a randomized controlled trial. Breast Cancer Res Treat, 135(3), 799-809. doi: 10.1007/s10549-012-2210-6

Wefel, J. S., Kesler, S. R., Noll, K. R., & Schagen, S. B. (2015). Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin, 65(2), 123-138. doi: 10.3322/caac.21258

Wefel, J. S., Saleeba, A. K., Buzdar, A. U., & Meyers, C. A. (2010). Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer, 116(14), 3348-3356. doi: 10.1002/cncr.25098

Feasibility and Acceptability of Computerized

Working Memory Training Program for Breast Cancer Survivors

Background and Significance:

Advances in breast cancer diagnosis and treatment have resulted in 3.5 million breast cancer survivors, the largest female cancer survivor group in the United States today (de Moor et al., 2013; Howlader N, April 2014.). Up to 1.32 million of the breast cancer survivors who received oncologic therapy report cognitive deficits as one of the challenging persistent symptoms (Ahles et al., 2002; Hurria et al., 2006; Jenkins et al., 2006; Meyers, 2000; Rugo & Ahles, 2003; Schagen et al., 1999; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Cognitive deficits adversely impact the breast cancer survivor's functional abilities, employment, and quality of life (Jansen, Cooper, Dodd, & Miaskowski, 2011). Functional cognitive deficits described by survivors include difficulties in finding words to express oneself; focusing and concentrating when reading a book or while driving; planning and executing tasks with multiple sequential steps such as following a recipe or paying bills; and organizing tasks (Boykoff, Moieni, & Subramanian, 2009; Frank, Vance, Jukkala, & Meneses, 2014; Myers, 2012; O'Shaughnessy, 2003; Wefel et al., 2004). These deficits adversely impact the ability to learn, self-confidence, interpersonal relationships, and the level of chronic distress, and also diminish the level of one's independence (Frank et al., 2014; Myers, 2012). Not all breast cancer survivors are affected; instead it a subgroup of survivors who experience persistent cognitive deficits (Ahles & Saykin, 2001; Mulrooney, 2008). The mechanisms of the persistent cognitive deficits are unclear and are probably multifaceted.

Objective cognitive deficits in working memory have been reported in breast cancer survivors compared to age-matched healthy control and cancer control groups (Ahles et al., 2010; Jansen et al., 2011; Noal et al., 2011; Quesnel, Savard, & Ivers, 2009). Working memory is critical to one's ability to temporarily hold information that is both verbal and visual-spatial; to remember what was just said in a conversation or what was read in a paragraph (Baddeley, 1987). It is also crucial to one's ability to focus, concentrate, comprehend, learn, reason, follow directions, and solve problems (Baddeley, 1987). Working memory is a mutable target to improve the symptoms related to cognitive deficits in breast cancer survivors.

Research evaluating interventions to treat working memory deficits in breast cancer survivors is limited (Barton et al., 2011; Ercoli et al., 2013; Ferguson et al., 2012; Kesler et al., 2013; Schuurs & Green, 2013; Von Ah et al., 2012). One potentially useful approach is in-home computerized training designed to improve working memory. This approach has been used in other populations with cognitive deficits, but we do not know if a scalable, computerized retraining program for working memory is feasible and acceptable in breast cancer survivors (Bigorra, Garolera, Guijarro, & Hervas, 2016; Conklin et al., 2015; Phillips et al., 2016; Sweeney et al., 2016; Vermeij et al., 2016). We also do not know the treatment dose tolerated, nor the efficacy dose of the intervention, as the doses of selected computerized memory related training vary in the studies to date (Ercoli et al., 2013; Hardy, Willard, Allen, & Bonner, 2013; Kesler et al., 2013; Von Ah et al., 2012).

The purpose of this study was to evaluate the feasibility, acceptability, and safety of an in-home, computerized, 6-week working memory training program in breast cancer survivors who self-report persistent cognitive deficits. The study used an existing computerized working memory intervention that has been successful in the treatment of working memory impairment in adults diagnosed with substance abuse, the elderly with mild cognitive impairments, and children with traumatic brain injury or brain cancer survivors (Bastien et al., 2003; Bender et al., 2008; Blacklock, Rhodes, Blanchard, & Gaul, 2010; Bower et al., 2000; Conklin et al., 2015). In addition, the training dose selected has been tested in populations who also experience fatigue, a common persistent symptom reported by breast cancer survivors (Bjorkdahl, Akerlund, Svensson, & Esbjornsson, 2013). Findings from this initial study will guide the planning of a larger randomized clinical trial to test this intervention, which could potentially be a practical and effective approach for addressing an important clinical problem.

Methods:

A randomized wait-list control trial research design was conducted from May 2016 through October 2016. Data were collected at baseline (T1) and at week 7-8 (T2). The purpose of the wait list control design was to provide participants access to the training program after T2 for ethical reasons. To help defray travel and parking costs, participants received total $100.00; $50.00 cash card after completion of measures at T1 and T2.

Recruitment and Screening:

Breast cancer survivors were recruited between May 2016 and October 2016 from a breast oncology clinic. Research study approval was obtained from the appropriate institutional review board. Participants who screened as eligible for the study and reported persistent cognitive deficits were referred by their primary breast oncologist to meet with the principal investigator during the clinic visit. Information about the study and consent forms were provided. Individuals who decided to participate were scheduled for an appointment to complete informed consent and T1 measures.

Study Sample and Setting

Recruitment and T1/T2 visits took place at a breast oncology clinic and research center near the clinic. All study participants were >18 years old; at least 18 months post oncologic treatments with surgery, chemotherapy and/or radiation therapy; diagnosed with stage 0, I, II, or III breast cancer, able to read, write, and speak English; agreed to travel for in-person baseline and post measures; had reliable, daily access to a computer with audio speakers and mouse; and self-reported cognitive memory impairments. Exclusion criteria included: history of multiple cancers; history of CNS disease, CNS radiation, intrathecal therapy, or CNS surgery; history of traumatic brain injury; neurologic disorders of stroke, encephalitis, dementia, Epilepsy, Alzheimer's disease, Parkinson's disease; self-report of learning disabilities; substance addiction; diagnosis of psychiatric disorders of psychosis, schizophrenia, or bipolar disorder; visual impairments such as uncorrected vision or color blindness; uncorrected hearing impairments; self-report that they are pregnant or planning to become pregnant in the next four months; anticipated moving from the region in the next 4 months; a Mini Mental State Exam (MMSE) score less than 19; previous participation in cognitive training program; and inability to use a mouse or computer keys to navigate on a computer screen.

Randomization: After completion of all baseline surveys, the MMSE, and neuropsychological tests, participants were randomized to the immediate intervention or wait list control group. A computerized algorithm was used to randomize participants based on age, PROMIS depression survey T-score, and level of education. The algorithm is based on the minimization method described by Pocock which is

based on an overall imbalance score that measures how far out of balance (within strata) the study is for a given set of random assignments (Pocock, 1983).

Intervention: The computerized working memory intervention was the Pearson Cogmed Working Memory Training Program Version 4.0 Cogmed[QM] (NCS Pearson Inc., Upper Saddle River, NJ). This program has eleven working memory exercises that rotate such that the training includes three to eight exercises a day (Pearson, 2014). A progress bar is visible on the top right of the computer screen during the training. The program is an adaptive training program; it becomes more difficult or less difficult depending on the subject's responses. Breast cancer survivors frequently report fatigue; thus, the Cogmed[QM] intervention dose tested in this study which has been successfully tested in other populations who report persistent fatigue (Bjorkdahl et al., 2013) was 5 days a week, up to 35 minutes a day, for 6 weeks. Participants linked to the online Cogmed training site using their personal computers to complete the training program. All participants received a coach phone call weekly to review training progress, to assess for symptom burden, safety, and to troubleshoot any technology difficulties. The researcher monitored intervention fidelity and dose each week as a part of the training progress review.

Measures:

Feasibility

Feasibility was assessed by tracking recruitment (eligible individuals invited versus enrolled), attrition between T1 and T2, number of weekly coach calls achieved, and reasons for declining to participate in the study.

Acceptability

Acceptability measures included adherence to the training schedule (5 days a week for 6 weeks), training completion (completing 24 of 30 assigned training blocks) (Pearson, 2014), a 100mm visual analog scale for ease of use and comprehensibility of program instructions; a 5 point Likert scale to rate satisfaction; and a 4 point Likert scale to rate if participants would recommend this computerized training program to breast cancer survivors with persistent cognitive deficits.

Safety

Safety was assessed and documented with each weekly coach phone call. Study participants were asked a specific question about symptoms, if any, that they were experiencing and if they felt the symptoms were related to the training. The participants were also asked a second question regarding any specific problems that they were experiencing related to the training over the past week. Participants were provided with a phone number to contact the researcher if at any time participants were experiencing issues or concerns.

Descriptive Measures

Participants completed several online surveys that provided relevant demographic information for the study. A demographic survey included date of birth, age, ethnicity, race, marital status, highest level of education completed, employment status, medication list and contact information. The Patient-Reported Outcome Measurement Information System, PROMIS, short forms for depression($\alpha = 0.98$) (Bowers, Waddell, & McCarthy, 2010), anxiety ($\alpha = 0.97$)(Avis, Ip, & Foley, 2006), and fatigue ($\alpha = 0.99$)(Avis et al., 2006) were also completed online. These specific symptom surveys were included as they have been strongly correlated with the self-report of perceived cognitive deficits in breast cancer survivors (Jenkins et al., 2006; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005).

Data Analysis

All baseline data (n=15) was included in the analysis. The post data analysis includes 13 participants. All descriptive statistics was performed using SPSS®, version 24 (IBM Corp, NY). Independent *t*-tests were performed between the intervention group and the waitlist control group for the variables of age, years of education, and PROMIS depression, anxiety, and fatigue short form T-scores and demonstrated no significant difference on these factors between groups.

Results

Sample Demographics

Fifteen female breast cancer survivors aged 43-65 (M = 54.7, SD = 6.5) consented to the study (See Table 1). Eighty percent (n=12) of the sample were Caucasian, 67% married or living with partner (n=10), and 60% employed full time (n=9). The breast cancer characteristics of the participants include 67% (n=10) having infiltrating ductal carcinoma, 47% (n=7) with Stage IIa/IIb breast cancer, 53% (n=8) having received combined oncologic treatments of surgery, chemotherapy, and radiation therapy, and 60% taking aromatase inhibitors (n=6) or selective estrogen receptor modulators (n=3) (See Table 1).

PROMIS surveys are scored using the re-centered item response theory item parameters. The scores are then transformed to a T-score metric (mean=50, SD=10). The three PROMIS symptom measures of anxiety, fatigue, and depression T-scores means were on average below the mean of 50 (see Table 1). Generally, the higher the T-scores, the higher the level of the symptom the participant is experiencing and these participants on average had lower levels of these three symptoms.

Feasibility

Of the 693 breast cancer survivors screened for eligibility, 70 survivors were medically eligible but only 27 (39%) reported persistent cognitive deficits. The study was presented to the 27 survivors and 15 (56%) agreed to participate in the study, or an average of 3 participants recruited and randomized a month. Of the 12 survivors who declined to participate in the study, 11 of them decided to not participate because the travel time and city traffic congestion and one survivor did not have a home computer or access to a computer. The study had an attrition rate of 13%, and all drop-outs were in the wait list control group (n = 2). Both participants were unable to reschedule for T2 measures due to personal life events would have required a minimum of a 4-week extension beyond the study protocol of 7-8weeks for T2 measures. All the participants in the wait-list group who completed T2 measures opted to complete the cognitive training program when provided the opportunity.

All the coach calls (n=78) were achieved, with 90% (70 calls) achieved with first call and remaining 10% (8 calls) achieved on 2nd or 3rd call on the same date. During the coach call adherence to the training schedule was evaluated.

Acceptability

Given that treatment group assignment was not expected to affect adherence once the intervention was started, and because participation in the intervention was very high in both groups, we analyzed the study groups together. Cogmed defines successful completion of the training program as 80% (24/30 blocks) of the six-week program which has a total of thirty training blocks. According to this criterion, adherence to the training program was high with all participants in both groups completing at least 24 blocks of training during the six-week training period. Six participants completed all 30 training blocks by 6 weeks, and 5 additional participants completed all 30 training blocks by week 7 (see Table 2). One of the immediate intervention participants completed 28 blocks during week #7 but stopped training due to an extended loss of her home internet service. One of the wait list control participants completed 25 blocks and then reported that she was not able to commit further time to training due to personal needs. This same participant completed both the acceptability survey and final coach call with a review of training summary.

The training protocol tested was a schedule of five days a week for six weeks, however participants in this study trained between two to six days a week over the six weeks of training. The first three weeks 63% in the immediate intervention group (n=5) and 80% in the wait list control (n=4) trained at least five days a week. There was a decrease noted during weeks four through six in both groups with 50% in the immediate intervention group (n=4) and 60% in the wait list control (n=3) training at least five days a week. Some of reasons participants shared for the week to week variation in training block accomplished included illness, unexpected travel for work, electrical outages and loss of internet connection due to storms, and too tired after work to train.

The participants trained an averaged 24 minutes (Wait List Control Group) to 32 minutes (Immediate Intervention Group) per training block which is less than the anticipated Cogmed^{QM} training protocol time of up to 35 minutes. The mean total training time for the immediate intervention group (830 minutes) is 139 minutes longer than the mean total training time for the wait list control group (691 minutes) (See Table 3).

The acceptability questionnaire was completed by all participants except for one person in the wait-list group (this group completed the survey after receiving an email with the on-line survey link rather than an in-person visit). The acceptability measures were high for ease of use (94.5) and clarity of training instructions (97.3) using a visual analog scale (0-100), and satisfaction was 4.92 on a 5 point Likert scale. During the week 6 coach call, participants were asked to rate on a four point Likert scale the likelihood of recommending this training program for other breast cancer survivors with cognitive deficits, and 100% of the participants responded that yes, they would "definitely recommend" the program.

Safety

There were no adverse events nor symptoms reported by participants during each of the coach calls. Mild cognitive fatigue was reported at the very end of training sessions during the first two weeks was reported by 62 % of participants. Participants shared that the cognitive fatigue quickly resolved, within a few minutes, after completing the training.

Discussion

This study explored the feasibility of an in-home online computerized working memory training program that asked participants to train 5 days a week for six weeks. Study results suggest that the study was feasible to implement and was safe with no adverse events reported. The positive acceptability outcomes in this study are similar to other studies using a computerized memory training intervention (Kesler et al., 2013; Krebs et al., 2010; Von Ah et al., 2012). This working memory training program was highly rated as easy to use, the training instructions were easy to understand and the participant satisfaction was very high. In addition, 100% of the participants would recommend this training program to for other breast cancer survivors.

Although 56% of the individuals who reported persistent cognitive deficits were recruited to the study, many of the other breast cancer survivors with persistent cognitive deficits were not able to participate in the study due to considerable travel distance required over mountain passes and bodies of water by ferries to receive oncology care at the breast oncology clinic. Both the travel costs (e.g. car ferry rides, or driving 3-4 hours over mountain passes with significant city traffic congestion) and travel time

required to return for two in person assessments at T1 and T2 were a barrier to recruitment. In a future clinical trial, the use of an on-line neuropsychological testing service (e.g. NIH Toolbox® for assessment of neurological and behavioral function or Cantab cognitive testing by Cambridge Cognition Ltd.) would eliminate the need for in person pencil and paper neuropsychological testing. Changing to an on-line neuropsychological testing in the study design would help to support recruitment by mitigating travel related issues and concerns.

Thirteen of fifteen participants completed the study, completed at least 24 training blocks, and all the wait list control group participants who completed T2 measures elected to participate in the computerized training program and completed the program. The completion rate of 80% was higher than two recently published studies testing in home use of Cogmed^{QM} training which reported from 50% to 78% completion rates (Conde et al., 2005; Conroy et al., 2013).

The difference in mean total active training time between the wait list control group (691 minutes) and the immediate intervention group (830 minutes) is due in part to 1) the lower mean training block time of the wait list control group (24 minutes) compared to the mean training block time of the immediate intervention group (32 minutes); 2) one participant in the immediate intervention group had a mean active training time of 45 minutes per training block which was 20 minutes longer than the mean active training time of 25 minutes of the other seven participants in the immediate intervention group; and 3) while one participant in each group completed less than 30 training blocks, the wait list control group participant completed 25 blocks compared to the immediate intervention group participant who completed 28 blocks, which is a difference of three training blocks of active training time. (See Table 3).

Intervention fidelity in this study had some opportunities for improvement in the participant instructions and understanding of the protocol they are asked to follow while training at home over 6 weeks as it relates to training 5 days a week for up to 35 minutes a day. For example, in a future study, some recommendations include: 1) use of a 6-week calendar for participants to document a proposed training plan may help to both set the expectation and provide a visual motivation for five day a week training schedule, 2) start all participants on a Monday for participants ease to determine that they have trained five days in the same week, and 3) allow for a 7 week training time window to account for life

events that may affect ability to participate in the rigorous training schedule. These recommendations would help to improve treatment fidelity for a future effectiveness research and would permit the comparisons of replicable treatments.

Some participants in the study used a touch pad or pen stylus instead of a mouse (n = 4). Some participants in the study used a touch pad or pen stylus instead of using a mouse per the training instructions (n = 4). In weekly coach calls, the reason offered for not using the mouse was the perception that one could respond faster using the touchpad or pen and therefore they would remember more of the number of letter sequences or the visual spatial responses required by the working memory exercises. Clicking with the mouse was perceived as slowing one's response time. Contributing to this preference of not using the mouse was that some participants did not fully understand and appreciate the meaning of the adaptive nature of the training despite explanation and demonstration on the computer at the time of registration to the training. Participants reported being very competitive, trying to get all the trials correct within each exercise and frustrated that they could not achieve more than 50% correct. After week 2, participants reported decreased frustration with the 50% or less success rate with each of the exercise trials. In addition, the participants learned to access the training summary that was graphed and depicted both their improvement and progress for each training exercise. Coach calls in the first two to three weeks included reinforcement about the adaptive design and purpose of the training; which was to train to improve their ability to store and manipulate verbal and visuospatial information, working memory.

In future efficacy study, an enhanced and more prescriptive participant education about the program needs to be included. For example, the rationale for strict protocol adherence needs to be included as part of the consent process and discussed at time participants are registered for the training. The research protocol also needs to consider real life events that occur during the training protocol time including storms resulting in multiple day loss of electricity, unexpected international travel for work, illness, unexpected internet loss for several days, and ferry boat break downs that delay study schedules.

Unlike previous studies using computerized cognitive training that focused on a single cognitive domain such as processing speed or executive function, this study utilized a cognitive training program that trains the complex system of working memory. In addition, this study utilized a licensed commercial

program that is cost effective (approx. $100.00 per person), easily scalable, and has a body of evidence using randomized control trial designs that suggest efficacy to increase working memory capacity.

Study Limitations and Research Implications

The study participants were primarily Caucasian women with at least 2-4 years of college education. The study needs to be replicated with a more demographically diverse group of breast cancer survivors.

Another consideration for future studies is to identify a computerized attention control for the wait list control group. A computerized attention control was explored; however, reports of the use of this control demonstrated significant participant dissatisfaction which resulted in significant study dropout rates. Alternative computer activity for the wait list control group needs to be explored. In addition, consideration of a weekly phone call from the research team may also help to improve the retention rate of the wait list control group.

Conclusion: This is the only study known to the authors to have used the Cogmed^{QM} in-home working memory training intervention in breast cancer survivors. The study demonstrated that an in-home computerized working memory intervention was feasible, acceptable, and safe with breast cancer survivors who are experiencing persistent cognitive deficits and supports the need for a larger randomized control study to evaluate efficacy of this intervention.

Table 1. Demographic Characteristics*
*No statistically significant difference between Immediate Intervention and Wait List Control groups for randomization characteristics.

Randomization Demographics	Mean	SD	Range
Age	54.67	6.54	43-65
Years of Education	14.8	2.34	12-19
PROMIS Depression T Score	44.48	6.58	36.9 - 57.8
PROMIS Anxiety T Score	47.54	7.74	41.6 - 67.3
PROMIS Fatigue T score	46.96	6.79	36.6 – 59.8

Demographic Characteristics	N
Gender	
Female	15
Male	0
Race or Ethnicity	
Caucasian	12
African American	2
Hispanic	1
Marital Status	
Never Married	1
Married/Living with Partner	10
Divorced	4
Employment	
Employed Full Time	9
Employed Part Time	3
Retired	1
Unemployed	2
Breast Cancer Type	
Infiltrating Ductal Carcinoma	11
Lobular Carcinoma	3
Mixed Infiltrating and Lobular	1
Breast Cancer Stage	
Stage 0	1
Stage IA	3
Stage IIA, IIB	7
Stage IIIA	4
Oncologic Treatment	
Surgery + Chemotherapy	2
Surgery + Chemo + Pertuzumab	2
Surgery + Chemo + Radiation	8
Surgery + Radiation	2
Surgery +Chemo+ Radiation+ Pertuzumab	1
Current Hormone Therapy	
Yes	9
No	6

Table 2. Computerized Working Memory Training Program Adherence and Performance by Group

Group	Total Weeks	Training Blocks Completed
Immediate Intervention (n=8)	6 weeks 7 weeks	30 blocks: n= 3 30 blocks: n= 4 One participant completed only 28 training blocks: n=1
Wait List Control (n-=5)	6 weeks 7 weeks	30 blocks: n=3 30 blocks: n=1 One participant completed only 25 training blocks: n=1

Table 3. Total Active Time Training by Group

Group	Total Active Training Time (minutes)
Immediate Intervention (n=8)	Mean Total Active Training Time= 830 minutes Range = 641 – 1358 minutes Mean training block time = 32 minutes per block
Wait List Control (n=5)	Mean Total Active Training Time = 691 min Range = 639 – 771 minutes Mean training block time = 24 minutes per block

References

Ahles, T. A., & Saykin, A. (2001). Cognitive effects of standard-dose chemotherapy in patients with cancer. *Cancer Invest, 19*(8), 812-820.

Ahles, T. A., Saykin, A. J., Furstenberg, C. T., Cole, B., Mott, L. A., Skalla, K., . . . Silberfarb, P. M. (2002). Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol, 20*(2), 485-493.

Ahles, T. A., Saykin, A. J., McDonald, B. C., Li, Y., Furstenberg, C. T., Hanscom, B. S., . . . Kaufman, P. A. (2010). Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol, 28*(29), 4434-4440. doi: 10.1200/jco.2009.27.0827

Avis, N. E., Ip, E., & Foley, K. L. (2006). Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for long-term cancer survivors in a sample of breast cancer survivors. *Health Qual Life Outcomes, 4*, 92. doi: 10.1186/1477-7525-4-92

Baddeley, A. (1987). *Working Memory*. New York: Oxford University Press.

Barton, D. L., Atherton, P. J., Bauer, B. A., Moore, D. F., Jr., Mattar, B. I., Lavasseur, B. I., . . . Loprinzi, C. L. (2011). The use of Valeriana officinalis (Valerian) in improving sleep in patients who are undergoing treatment for cancer: a phase III randomized, placebo-controlled, double-blind study (NCCTG Trial, N01C5). *J Support Oncol, 9*(1), 24-31. doi: 10.1016/j.suponc.2010.12.008

Bastien, C. H., Fortier-Brochu, E., Rioux, I., LeBlanc, M., Daley, M., & Morin, C. M. (2003). Cognitive performance and sleep quality in the elderly suffering from chronic insomnia. Relationship between objective and subjective measures. *J Psychosom Res, 54*(1), 39-49.

Bender, C. M., Pacella, M. L., Sereika, S. M., Brufsky, A. M., Vogel, V. G., Rastogi, P., . . . Ryan, C. M. (2008). What do perceived cognitive problems reflect? *J Support Oncol, 6*(5), 238-242.

Bjorkdahl, A., Akerlund, E., Svensson, S., & Esbjornsson, E. (2013). A randomized study of computerized working memory training and effects on functioning in everyday life for patients with brain injury. *Brain Inj, 27*(13-14), 1658-1665. doi: 10.3109/02699052.2013.830196

Blacklock, R., Rhodes, R., Blanchard, C., & Gaul, C. (2010). Effects of exercise intensity and self-efficacy on state anxiety with breast cancer survivors. *Oncol Nurs Forum, 37*(2), 206-212. doi: 10.1188/10.onf.206-212

Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2000). Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol, 18*(4), 743-753.

Bowers, J. M., Waddell, J., & McCarthy, M. M. (2010). A developmental sex difference in hippocampal neurogenesis is mediated by endogenous oestradiol. *Biol Sex Differ, 1*(1), 8. doi: 10.1186/2042-6410-1-8

Boykoff, N., Moieni, M., & Subramanian, S. K. (2009). Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. *J Cancer Surviv, 3*(4), 223-232. doi: 10.1007/s11764-009-0098-x

Conde, D. M., Pinto-Neto, A. M., Cabello, C., Santos-Sa, D., Costa-Paiva, L., & Martinez, E. Z. (2005). Quality of life in Brazilian breast cancer survivors age 45-65 years: associated factors. *Breast J, 11*(6), 425-432. doi: 10.1111/j.1075-122X.2005.00124.x

Conklin, H. M., Ogg, R. J., Ashford, J. M., Scoggins, M. A., Zou, P., Clark, K. N., . . . Zhang, H. (2015). Computerized Cognitive Training for Amelioration of Cognitive Late Effects Among Childhood Cancer Survivors: A Randomized Controlled Trial. *J Clin Oncol*. doi: 10.1200/jco.2015.61.6672

Conroy, S. K., McDonald, B. C., Smith, D. J., Moser, L. R., West, J. D., Kamendulis, L. M., . . . Saykin, A. J. (2013). Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. *Breast Cancer Res Treat, 137*(2), 493-502. doi: 10.1007/s10549-012-2385-x

de Moor, J. S., Mariotto, A. B., Parry, C., Alfano, C. M., Padgett, L., Kent, E. E., . . . Rowland, J. H. (2013). Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev, 22*(4), 561-570. doi: 10.1158/1055-9965.epi-12-1356

Ercoli, L. M., Castellon, S. A., Hunter, A. M., Kwan, L., Kahn-Mills, B. A., Cernin, P. A., . . . Ganz, P. A. (2013). Assessment of the feasibility of a rehabilitation intervention program for breast cancer

survivors with cognitive complaints. *Brain Imaging Behav, 7*(4), 543-553. doi: 10.1007/s11682-013-9237-0
Ferguson, R. J., McDonald, B. C., Rocque, M. A., Furstenberg, C. T., Horrigan, S., Ahles, T. A., & Saykin, A. J. (2012). Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. *Psychooncology, 21*(2), 176-186. doi: 10.1002/pon.1878
Frank, J. S., Vance, D. E., Jukkala, A., & Meneses, K. M. (2014). Attention and memory deficits in breast cancer survivors: implications for nursing practice and research. *J Neurosci Nurs, 46*(5), 274-284. doi: 10.1097/jnn.0000000000000078
Hardy, K. K., Willard, V. W., Allen, T. M., & Bonner, M. J. (2013). Working memory training in survivors of pediatric cancer: a randomized pilot study. *Psychooncology, 22*(8), 1856-1865. doi: 10.1002/pon.3222
Howlader N, N. A., Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). . (April 2014.). *SEER Cancer Statistics Review, 1975-2011,*. Retrieved from http://seer.cancer.gov/csr/1975_2011/.
Hurria, A., Goldfarb, S., Rosen, C., Holland, J., Zuckerman, E., Lachs, M. S., . . . Hudis, C. (2006). Effect of adjuvant breast cancer chemotherapy on cognitive function from the older patient's perspective. *Breast Cancer Res Treat, 98*(3), 343-348. doi: 10.1007/s10549-006-9171-6
Jansen, C. E., Cooper, B. A., Dodd, M. J., & Miaskowski, C. A. (2011). A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. *Support Care Cancer, 19*(10), 1647-1656. doi: 10.1007/s00520-010-0997-4
Jenkins, V., Shilling, V., Deutsch, G., Bloomfield, D., Morris, R., Allan, S., . . . Winstanley, J. (2006). A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer, 94*(6), 828-834. doi: 10.1038/sj.bjc.6603029
Kesler, S., Hadi Hosseini, S. M., Heckler, C., Janelsins, M., Palesh, O., Mustian, K., & Morrow, G. (2013). Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clin Breast Cancer, 13*(4), 299-306. doi: 10.1016/j.clbc.2013.02.004
Krebs, E. E., Bair, M. J., Damush, T. M., Tu, W., Wu, J., & Kroenke, K. (2010). Comparative responsiveness of pain outcome measures among primary care patients with musculoskeletal pain. *Med Care, 48*(11), 1007-1014. doi: 10.1097/MLR.0b013e3181eaf835
Meyers, C. A. (2000). Neurocognitive dysfunction in cancer patients. *Oncology (Williston Park), 14*(1), 75-79; discussion 79, 81-72, 85.
Mulrooney, T. (2008). Cognitive impairment after breast cancer treatment. *Clin J Oncol Nurs, 12*(4), 678-680. doi: 10.1188/08.cjon.678-680
Myers, J. S. (2012). Chemotherapy-related cognitive impairment: the breast cancer experience. *Oncol Nurs Forum, 39*(1), E31-40. doi: 10.1188/12.onf.e31-e40
Noal, S., Levy, C., Hardouin, A., Rieux, C., Heutte, N., Segura, C., . . . Joly, F. (2011). One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys, 81*(3), 795-803. doi: 10.1016/j.ijrobp.2010.06.037
O'Shaughnessy, J. (2003). Chemotherapy-related cognitive dysfunction in breast cancer. *Semin Oncol Nurs, 19*(4 Suppl 2), 17-24.
Pocock, S. J. (1983). *Clinical Trials: A practical approach*: John Wiley and Sons Ltd.
Quesnel, C., Savard, J., & Ivers, H. (2009). Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. *Breast Cancer Res Treat, 116*(1), 113-123. doi: 10.1007/s10549-008-0114-2
Rugo, H. S., & Ahles, T. (2003). The impact of adjuvant therapy for breast cancer on cognitive function: current evidence and directions for research. *Semin Oncol, 30*(6), 749-762.
Schagen, S. B., van Dam, F. S., Muller, M. J., Boogerd, W., Lindeboom, J., & Bruning, P. F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer, 85*(3), 640-650.
Schuurs, A., & Green, H. J. (2013). A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. *Psychooncology, 22*(5), 1043-1049. doi: 10.1002/pon.3102
Shilling, V., Jenkins, V., Morris, R., Deutsch, G., & Bloomfield, D. (2005). The effects of adjuvant chemotherapy on cognition in women with breast cancer--preliminary results of an observational longitudinal study. *Breast, 14*(2), 142-150. doi: 10.1016/j.breast.2004.10.004

Von Ah, D., Carpenter, J. S., Saykin, A., Monahan, P., Wu, J., Yu, M., . . . Unverzagt, F. (2012). Advanced cognitive training for breast cancer survivors: a randomized controlled trial. *Breast Cancer Res Treat, 135*(3), 799-809. doi: 10.1007/s10549-012-2210-6

Wefel, J. S., Lenzi, R., Theriault, R. L., Davis, R. N., & Meyers, C. A. (2004). The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer, 100*(11), 2292-2299. doi: 10.1002/cncr.20272

A randomized pilot trial of a computerized working memory intervention for cognitive impairment in breast cancer survivors

Introduction

Cognitive impairments are one of the most troubling persistent and late effects of oncologic treatment(s) experienced by breast cancer survivors.[1-5] Since the 1990's there is an ever-growing body of evidence of cognitive impairments in individuals with breast cancer including neuropsychological test studies, [2,6-8] neuroimaging studies,[9-12] and symptom self-report studies including the impact and interference with daily function and quality of life.[13-16] The prevalence of cognitive impairments reported in studies that performed neuropsychological tests ranges from 13-70%.[2,6,7,17-24] This wide prevalence range is related to methodologic differences of research studies. These studies have demonstrated deficits in the cognitive domains of working memory, including verbal memory, visual memory and executive function both prior to and after oncologic treatments. [4,25]

Working memory is the cognitive process characterized by functioning over a few seconds at a time, serving as temporary storage of information, manipulating the information, and helping to focus one's attention.[26] The Baddeley Working Memory Model includes the cognitive functions of visuo-spatial working memory, verbal working memory (phonological), and executive function.[26] Visuo-spatial memory refers to the neural loop process which supports the ability to understand and conceptualize visual representation and spatial relationships when performing a task.[26] Verbal working memory refers to the neural loop process that temporarily holds words to keep them in mind.[26] Executive function is a set of higher order cognitive processes that serves as a temporary store, keeping information available needed for current reasoning processes.[26] The two neural loops of verbal working memory and visuo-spatial memory interact in feedback loops with the executive function. Working memory is key to an individual's attention and learning abilities.

Both the etiologies and treatments of cognitive impairments are not well established.[1] Research is needed to determine efficacious interventions to treat persistent impairments in cognitive function for survivors following treatment for breast cancer. The purpose of this manuscript is to report on the evaluation of the differences in posttest (T2) adjusted for baseline (T1) means for neuropsychological tests and Patient-Reported Outcomes Measurement Information System, PROMIS®, short form self-

report surveys and Functional Assessment of Cancer Therapy Cognition (version 3) (FACT-Cog) self-report survey between the intervention group and wait control group.

Methods

Design Overview

A randomized control pilot trial was conducted May 2016 through October 2016 and included a total sample of 15 breast cancer survivors. Figure 1 displays the patient flow through the study.

Enrollment of Participants

Participants were recruited from a comprehensive cancer center breast health clinic. Eligibility criteria included 18 years of age or older; able to read, write and speak English; have reliable internet connection and daily access to a computer with audio/speakers and a mouse; and agreed to travel for two in person assessments during the research study. Participants with were diagnosed with stage 0,1,2, or 3 breast cancers, were 18 months to five years post primary oncologic treatment for breast cancer including surgery, radiation, and/or chemotherapy and included individuals currently receiving selective estrogen receptor modulators or aromatase inhibitors.

Participants were not eligible if their medical history included diagnosis of more than one cancer; a history of central nervous system disease, surgery, radiation, or intrathecal therapy; a history of traumatic brain injury; neurological disorders of stroke, encephalitis, dementia, Alzheimer's disease, Parkinson's disease; self–report of learning disabilities, previous participation in cognitive training program, color blindness, or uncorrected visual or hearing impairments or substance addiction; diagnosis of diagnosis of psychiatric disorders of psychosis, schizophrenia, or bipolar disease; anticipate that they will move out of the geographic region in the next 4 months; a Mini Mental State Exam score less than 19; and inability to use a mouse when using the computer.

Research study approval was obtained from the appropriate institutional review board (IRB). A partial waiver of consent and HIPPA waiver were granted by the IRB so that the investigator could pre-screen potential participants prior to clinic visit. The eligible potential participant list was provided to the oncologists prior to the scheduled breast clinic for review. At the clinic visit, oncologists asked potential participants if they were experiencing persistent cognitive or memory symptoms. If the response was positive for persistent cognitive or memory symptoms, then the oncologist provided brief information

about the study. Potential participants who wanted to learn more about the study were referred to the investigator who was available in the clinic to meet following the provider visit. Information about the study was provided and questions were answered. Potential participants who were interested to participate in the study were provided consent forms and scheduled for an appointment to complete informed consent and baseline (T1) measures.

Procedures

At the consent and baseline measures appointment, participants completed both on-line self-report surveys using a PC computer and mouse and a battery of paper and pencil neuropsychological tests. Next, participants were randomized to the wait list control or immediate intervention groups using a computerized program that included a minimization randomization algorithm using the participant's age, PROMIS® depression short form T-score, and level of education. Participants randomized to the wait list control group were scheduled for a return in-person appointment to complete post measures at seven to eight weeks. At the week seven or eight post visit, wait list control group participants were offered the opportunity to participate in the working memory training program.

Participants randomized to the immediate intervention group were registered for the Cogmed^{QM} working memory training program on-line and the opportunity to practice the training exercises in a practice domain on the registration site. The Cogmed^{QM} program provides a unique user ID and password that does not include any patient identifiers. The immediate intervention participants received a paper copy of the Cogmed program log in instructions and an email with the instructions. The Immediate Intervention group were also scheduled to return in seven to eight weeks for post measures. The Cogmed training program was provided at no cost to participants.

Participants were provided with a $50.00 VISA cash card at T1 and T2 after completion of all measures. The funds were provided to help to defray travel and parking costs. The primary investigator enrolled participants into the study, completed all baseline (T1) and post (T2) measures with patients, and conducted all the coach phone calls while participants were enrolled in the intervention.

Measures

REDcap™ was the web-based data platform used to design and build the self-report study surveys used in the study. PROMIS® (Patient-Reported Outcomes Measurement Information System) is

a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions symptom surveys and the Fact-Cog V3 surveys were directly downloaded into REDcap™. The auto-scoring feature for PROMIS® symptom surveys was utilized for the Depression Short Form survey.

Patient-Reported Outcomes Measurement Information System (PROMIS®) surveys

PROMIS® measures may be utilized to evaluate and monitor physical, neurocognitive, and social health in adults and children. The five PROMIS® short form measures administered at T1 and T2 in this study were anxiety (α= 0.97),[27] depression (α= 0.98),[28] fatigue (α= 0.99),[27] applied cognition general concerns (α= 0.98),[29] and applied cognition executive function (α= 0.98).[29] The eight question short forms were used. The PROMIS® measure raw scores are transformed to a T score metric (mean = 50, standard deviation=10). The HealthMeasures Scoring Service (https://www.assessmentcenter.net) was used to score each of the PROMIS® measures.

Functional Assessment of Cancer Therapy Cognition (FACT-Cog) (version 3)

The FACT-Cog survey includes 37 questions and consists of four subscales; perceived cognitive impairments, comments from others, perceived cognitive abilities, and impact on quality of life.[30] Participants are asked to respond to statements about cognitive function symptoms as it applies to the past seven days. The perceived cognitive impairment (CogPCI), impact of perceived cognitive impairments on quality of life (CogQOL) and comments from others (CogOth) subscales are negatively worded statements. The higher the score for the CogPCI, CogQOL, and the CogOth subscales, the less cognitive symptom burden the individual is experiencing. The perceived cognitive abilities (CogPCA) questions are positively worded statements. The lower the score for this subscale, the higher cognitive ability symptoms burden the individual is experiencing.

Neuropsychological Tests

The seven neuropsychological tests administered by the primary investigator at T1 and T2 with paper and pencil were the Rey Auditory Verbal Learning Test (RAVLT); Wechsler Adult Intelligence Scale-IV (WAIS-IV) Symbol Search and Coding tests; Delis-Kaplan Color-Word Interference Test with four conditions; Trail Making A test; Trail Making B test; and the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Letter-Number Sequencing test. All seven tests have moderate to high reliability reported.[31-35]

The same version of each test was used at T1 and T2. One purpose of the wait list control design was to be able to evaluate practice effects since the repeated measures were performed in a relatively short time span of seven to eight weeks.

Intervention

The intervention utilized in this study was the adult Cogmed[QM] Version 4.0 computerized working memory program (NCS Pearson Inc., Upper Saddle River, New Jersey). The training program selected for this study was an adaptive training program consisting of training five days a week for six weeks. Participants train for up to 35 minutes a day, five days a week on three to eight different working memory training exercises in their own home using their own personal computer or Apple® computer. Each exercise has multiple trials. The trials become more difficult or less difficult depending on the participant's response success with the previous trial. This specific training protocol has been feasible and acceptable in other populations who experience the symptom of persistent fatigue.[36] Many breast cancer survivors experience persistent symptoms of fatigue, thus the 5 day a week for 6 week training protocol was selected. In addition, to the training, participants receive a weekly coach phone call to review training progress and troubleshoot any technological difficulties.

Statistical Analysis

The baseline line data (n=15) for all participants was included in the analysis. The difference score (posttest scores adjusted for baseline scores) analysis included data from participants who completed the study (n=13). Descriptive statistics, comparison of means, and nonparametric Mann-Whitney U analysis was completed using SPSS Statistics 24®.

The FACT-Cog -V3 survey has four subscales that are reported; perceived cognitive impairment (CogPCI), perceived cognitive impairments on quality of life(CogQOL), comments from others subscale (CogOth), and perceived cognitive abilities subscale (CogPCA). The CogPCI and the CogPCA subscales include two questions each that were added after the initial validation analysis of this measure. The author of the measure recommends that Cronbach's alpha and individual item-score correlation coefficient analysis be conducted to determine if the scores of these four questions should be included in the subscale scores. The analysis of PCI 18 question version (α = 0939) and the 20-question version (α =0.938) as well as the individual item score correlations suggest that the 20-question version is a good fit

and thus the PCI 20 question version is reported in the study results. Both the analysis of the CogPCA subscale seven question version (α =0.887) and the nine-question version (α=0.914) as well as the review of the individual item-score correlation coefficient analysis suggests that the nine-question version is a good fit. Thus, the nine-question version is reported in the study results.

Results

Participant Characteristics

Baseline demographic and medical data are summarized in Table 1 and Table 2. Participants were all female, age 43-65 (M = 55, SD = 7), Caucasian (80%), married or living with a partner (67%), employed full time (60%) and highly educated (73% > high school). The most common type of breast cancer was infiltrating ductal carcinoma (73%) and stage IIA or IIB (47%). The most common oncologic treatment combination was surgery, chemotherapy, and radiation (53%). Some participants were prescribed hormonal therapy treatment with selective estrogen receptor modulators or aromatase inhibitors (60%).

Intervention Results

Cogmed^{QM} defines completion of the training program as 80% of the training protocol sessions completed which for this study is 24 training sessions.[37] All immediate intervention group (n=8) and wait list control group (n=5) who participated in the in-home computerized working memory training completed between 25 -30 training sessions. An indicator of training progress for the Cogmed^{QM} program is the training index score. The study participant's working memory performance index score mean baseline start scores for the two groups were wait list control (M=84.6, SD= 12.8) and immediate intervention group (M= 87.5, SD = 5.58). The maximum performance index score mean improvement for two groups were wait list control (M= 115.8, SD=14.13) and immediate intervention (M=109.88, SD=7.64). The change index score for the two groups, wait list control (M= 31.20, SD=11.99) and immediate intervention (M=23, SD=4.41).

Group Baseline Comparisons

Demographics

The wait list control (n=7) and immediate intervention (n=8) groups were compared using non-parametric Mann Whitney U analysis on demographic variables and baseline PROMIS® short form symptom surveys, FACT-Cog subscales, and Neuropsychological test scores. The demographic variables

analyzed were age, years of education, and time in months since final oncologic treatment. No significant difference was found between the wait list control group and the immediate intervention group for the demographic variables of age, education, and time (in months) since final oncologic treatment (See Table 1).

PROMIS® Symptom Short Form Surveys and FACT-Cog Survey

The non-parametric analysis, Mann Whitney U, was performed between the wait list control group and the immediate intervention group self-report baseline measures (PROMIS® symptom surveys and the FACT Cog subscales) and the results demonstrated no significant difference for anxiety, fatigue, depression, applied cognition general concerns, applied cognition executive function, FACT-Cog Perceived Cognitive Impairment subscale, FACT-Cog Comments from Others subscale, and the FACT-Cog Perceived Cognitive Abilities (See table 3). There was a statistically significant difference for the FACT-Cog Quality of Life subscale between the wait list control group (M=13.00, SD=2.77) and the immediate intervention (M=8.5, SD=4.38); U (n_{II} =8, n_{WLC}=5) = 9.5. Z= -2.154, p_{exact}=.029. The FACT-Cog Quality of Life subscale has a score range of 0-16 (see Table 3). The higher the score, the better the quality of life. Thus, the immediate intervention group reported lower quality of life scores at baseline compared to the wait list control group.

Neuropsychological Tests

The Rey Auditory Verbal Learning Test (RAVLT) includes four primary measures including Total Word Trials, Immediate Recall condition, Delay condition, and Recognition. The raw score values were used to compare groups for the baseline RAVLT test. Non-parametric analysis revealed no significant difference in the baseline mean raw scores for the Total Words Trials 1 through 5, immediate recall, delay, nor recognition (see Table 4).

The WAIS IV symbol search, coding, letter number sequencing tests and the DKEF's Color Block test are reported as scaled scores. Each test uses a different combination of age, race, education in years to derive a scaled score from the raw scores. The scaled score values were used to compare the groups baseline measures for these four tests. There was no significant difference in the baseline scale scores for the WAIS IV symbol search, coding, letter number sequencing tests and the DKEF's Color Block test (see Table 4).

Baseline Measure Differences Between Participants Completing and not Completing the Study

The mean PROMIS® T scores for anxiety, fatigue, depression, and applied cognition general concerns of the participants who did not complete the study were comparable to the immediate intervention group mean T scores except for the applied cognition executive function which was comparable to the wait list control T score mean (See Figure 2).

The FACT-Cog subscale means for the subscales CogPCI, CogQOL, CogOth of the study participants who did not complete the study were comparable to both the immediate intervention group and the wait list control group. There was a difference noted for the perceived cognitive abilities (Cog PCA) subscale mean score with both the wait list control and immediate intervention group scores were higher (M=17.63, SD=7.07) compared to the two participants who did not complete the study (M=20.00, SD 7.30) suggesting that these two participants were experiencing on average, lower perceived cognitive abilities symptom burden compared to the wait list control and immediate intervention groups.

Finally, the neuropsychological test results for both study participants who did not complete the study were some of the lowest scaled scores for selected tests compared to the wait list control and intervention groups on immediate memory span and new learning (Rey Auditory Verbal Learning Test) executive function (D-KEFS color word test-conditions 1, 2,3), processing speed and visual attention (WAIS IV Symbol Search and Coding) and working memory and verbal memory (WAIS IV Letter Number Sequencing Test) compared the immediate intervention and wait list control groups.

Difference in posttest (T2) adjusted for baseline (T1)

The primary aims of this study were to analyze the difference between the posttest means at week seven to eight adjusted for baseline means for the PROMIS® symptom measures, the FACT-Cog measure, and the Neuropsychological tests (Rey Auditory Verbal Learning Test; WAIS IV Symbol Search, Coding, and Letter Number Sequencing; and DKEF Color Word test). A Mann-Whitney test indicated that there was difference with the PROMIS® applied cognition general concern measure, U (n_{II} = 8, n_{WLC} = 5) = 5.0, Z= -2.196, p_{exact} = .030. with the immediate intervention group demonstrating a greater decrease in cognitive general concerns compared to the wait list control group. The PROMIS® Applied Cognition Executive Function measure also demonstrated a difference U(n_{II} = 8, n_{WLC} = 5) = 4.0, Z= -

2.34,p_{exact} =.019 with a greater decrease in the executive function related symptoms compared to the wait list control group. The FACT-Cog survey also indicated there was a difference for three of the subscales: CogPCI U(n_{II} = 8, n_{WLC} = 5)=5.0, Z= -2.202, p_{exact} = .030; CogQOL U(n_{II} = 8, n_{WLC} = 5)=4.5, Z= -2.291, p_{exact} = .022; and CogPCA U(n_{II} = 8, n_{WLC} = 5)= 3.5, Z= -2.422, p_{exact} =.011; with the intervention group demonstrating a greater decrease in perceived cognitive impairments (CogPCI), impact of perceived cognitive impairments on quality of life (CogQOL) and perceived cognitive abilities (CogPCA) compared to the wait list control group (see Table 5). There were no differences identified for posttest the seven neuropsychological test results adjusted for baseline between the wait list control and the immediate intervention groups (See Table 6). There was however, a small trend in the difference scores for the scaled score neuropsychological tests with the immediate intervention group with small scaled score improvements compared to the wait list control group (See Figure 3).

Discussion

In this study, we tested the effects of conducting a randomized control trial of an in-home computerized working memory intervention for breast cancer survivors who were experiencing persistent cognitive impairments at > 18 months post oncologic therapies. A computerized minimization randomization algorithm was utilized to randomize study participants using the factors of age, PROMIS® Depression short form T score, and level of education and analysis demonstrated no statistically significant difference between groups for these characteristics. However, there were other medical characteristics for which the two groups were different including type of hormone therapy, length of time since last oncologic therapy, and type of oncologic treatment.

Sixty percent of the study participants were taking hormone therapy during the study. The immediate intervention group (n=6) were primarily prescribed Tamoxifen (n= 4) (67%) and Aromatase Inhibitors (n=2) (66%) and Tamoxifen (n=1) (33%). A recent study provided evidence that breast cancer survivors taking Tamoxifen have been shown to have significant deficits in working memory and executive function performance.[38] The type of hormone therapy may have a moderating effect on the neurocognitive outcomes and may be an important factor to include in the randomization algorithm.

The immediate intervention and wait list control groups were not statistically significantly different for the characteristic of time (months) since oncologic treatment, but they trended toward significance.

The wait list control group had a mean of 10 months less time since final oncologic therapy administration compared to the immediate intervention group. Neuroimaging studies have suggested that cognitive recovery occurs in breast cancer survivors and stabilizes in the first 1-2 years after treatment.[25] Conversely, longitudinal studies have shown that for a subset of breast cancer survivors, they in fact do not experience this recovery and stabilization effect but instead approximately 30% experience persistent cognitive impairments even at 10 and 20 year follow-up.[39] Therefore, including the months since last treatment as a randomization factor may help balance the groups for the cognition maturation factor.

The two study participants who were treated with either Surgery, Chemotherapy, and Pertuzumab or Surgery, Chemotherapy, Radiation and Pertuzumab were both in the wait list control group. These regimens are lengthy treatments that might have an impact on symptoms depression, anxiety, and fatigue which are often associated with cognitive impairments.[5,22]

The working memory training program is rigorous, five days a week, 35 minutes each day, for six weeks. All 13 participants who started the training program completed the program and were available for weekly coach phone calls with the researcher. The participants were all engaged with the training as evidenced by improvements in the training index scores as demonstrated by the mean change index score improvements for the wait list control (M= 31.20) and immediate intervention (M=23).

The analysis of the posttest measure scores adjusted for baseline measure scores (difference scores) revealed selected self-report symptom measures that were statistically significant. The PROMIS® applied cognition general concerns survey difference results demonstrated a decrease in general concerns about one's cognitive abilities for the immediate intervention group compared to the wait list control group. This survey asks questions about the frequency over the past 7 days that one has experienced trouble forming thoughts, slowed thinking, trouble concentrating, inability to pay attention, brain not working well, having to work harder to stay focused on what one is doing, trouble shifting back and forth between different activities that require thinking, and cognitive impairment interference with quality of life. The PROMIS® applied cognition executive function survey difference results also demonstrated a decrease in executive function symptom burden for post measures adjusted for baseline for the immediate intervention group compared to the wait list control group. The survey asks questions about the frequency over the past 7 days that one has had difficulty checking accuracy of financial bank

statements/bills, counting money when making purchases, reading and following complex instructions, planning and keeping appointments, managing time to complete daily activities, managing complicated tasks, organizing important personal papers such as bills, and learning new tasks. A higher T score on both measures indicates that the participant has fewer cognitive concerns. On each of these itemized questions, the immediate intervention group symptoms improved or stayed constant whereas the wait list control group stayed constant or symptoms worsened from baseline (T1) to posttest (T2). The neuropsychological tests did not demonstrate this trend of improvement but from the immediate intervention participant's perspective, general concerns about cognitive deficits and executive function abilities had overall improved.

The FACT-Cog subscales of perceived cognitive impairment (20 questions), impact of perceived cognitive impairments on quality of life (4 questions), and perceived cognitive abilities (9 questions) scaled scores for posttest adjusted for baseline were statistically significant. The lower the score, the higher the symptom burden for all three of these subscales. The wait list control group subscale scores were lower or stable in the post assessment compared to the baseline assessment for all the subscales. The immediate intervention group posttest subscale scores all increased with one exception of one participant for the CogPCA subscale score. The increase in the scores ranged from seven to thirty-nine points for the CogPCI subscale score; from two to nine points for the CogQOL subscale score and from six to fifteen points for the CogPCA subscale score for the immediate intervention group. One immediate intervention group participant had a post adjusted score that was a three-point decrease from baseline. In general, the participants in the immediate intervention group experienced an improved quality of life related to cognitive concerns, and had less perceived cognitive impairment and perceived cognitive ability symptom burden.

These findings for the PROMIS® and Fact-Cog subscales demonstrate that the intervention group reported improvements in their cognitive performance after completing the training program. The intervention provided real time feedback on training progress and the weekly coach calls also summarized training progress and evaluated and resolved any computer technology issues or concerns. The study was not powered for efficacy; however, these findings suggest there are some neurocognitive benefits and supports the need for further research.

There were no differences noted for the seven neuropsychological test results between the wait list control and immediate intervention groups. There is a small trend of improvement for the immediate intervention group with all post test scores adjusted for baseline demonstrating a 0.75 to 2.375 scaled score improvement in the neuropsychological test results. The wait list control group however decreased cognitive performance scores for selected tests (e.g. DKEFs Condition 2, WAIS IV Letter Number Sequencing); demonstrated no change for DKEFs condition 1, DKEFs condition 3, and DKEFS condition 4; and increased slightly for WAIS IV Symbol, Coding and Trails A and B. It is possible that the slight improvements seen in the wait list control group results (see Figure 3) and some of the intervention group improvements may represent practice effects since the same neuropsychological tests were used at both baseline and posttest assessments.

Future Recommendations

Changes recommended for a larger randomized control trial to evaluate efficacy of the in-home computerized working memory training intervention would include: blinding of the research team members who perform the weekly coach calls and who complete the posttest measures with study participants; inclusion of an attention control condition and a weekly phone call to the wait list control group during the wait period (six to seven weeks), and adding additional medical characteristics to the randomization algorithm such as oncologic therapy treatment types, time (months) since oncologic treatment, and hormonal therapy (yes, no).

Conclusion:

The preliminary results of this pilot study support moving forward with a larger scale randomized control trial that should include a more demographically diverse population of breast cancer survivors and will be powered to evaluate efficacy of an in-home computerized working memory training program. An evidence based in-home computerized treatment for persistent working memory cognitive impairments in breast cancer survivors could improve quality of life and function for this survivor population.

Figure 1. Study Flow Diagram

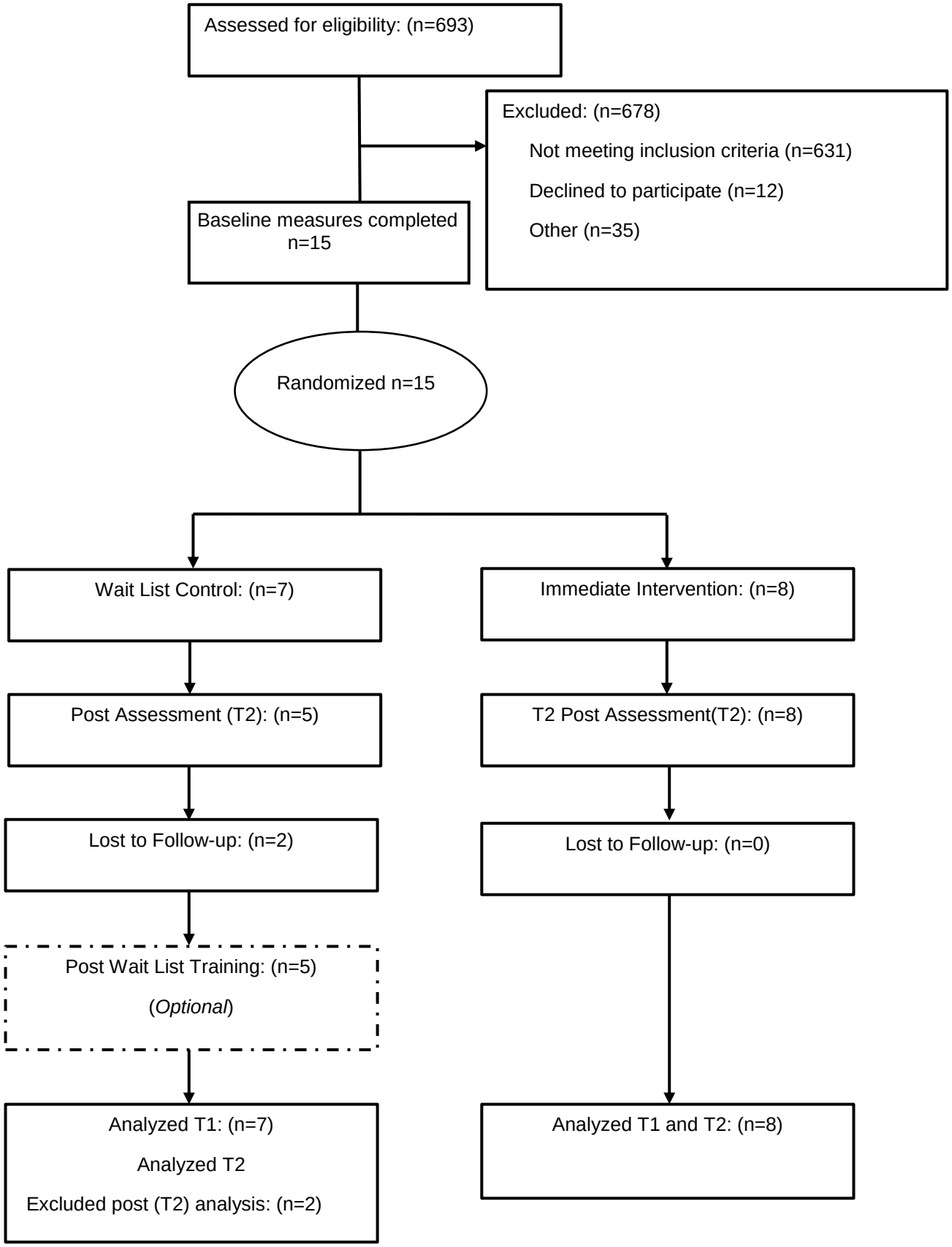


Figure 2. Baseline PROMIS® T Score Means between Wait List Control, Immediate Intervention, and Study Participants who did not Complete the Study

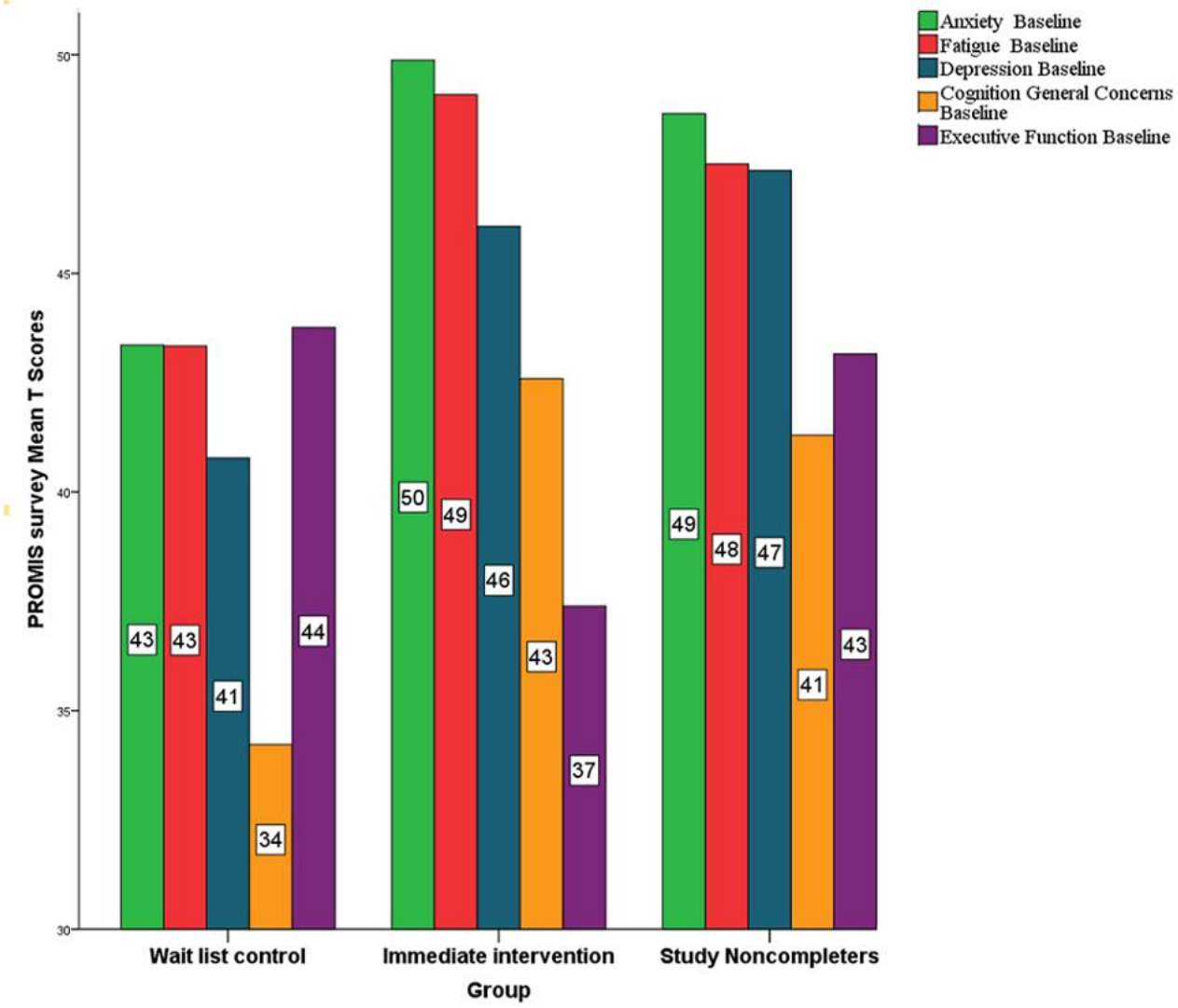


Figure 3. Posttest Mean Scaled Score adjusted for Baseline Mean Scaled Scores (Differences) of Neuropsychological Tests by Group

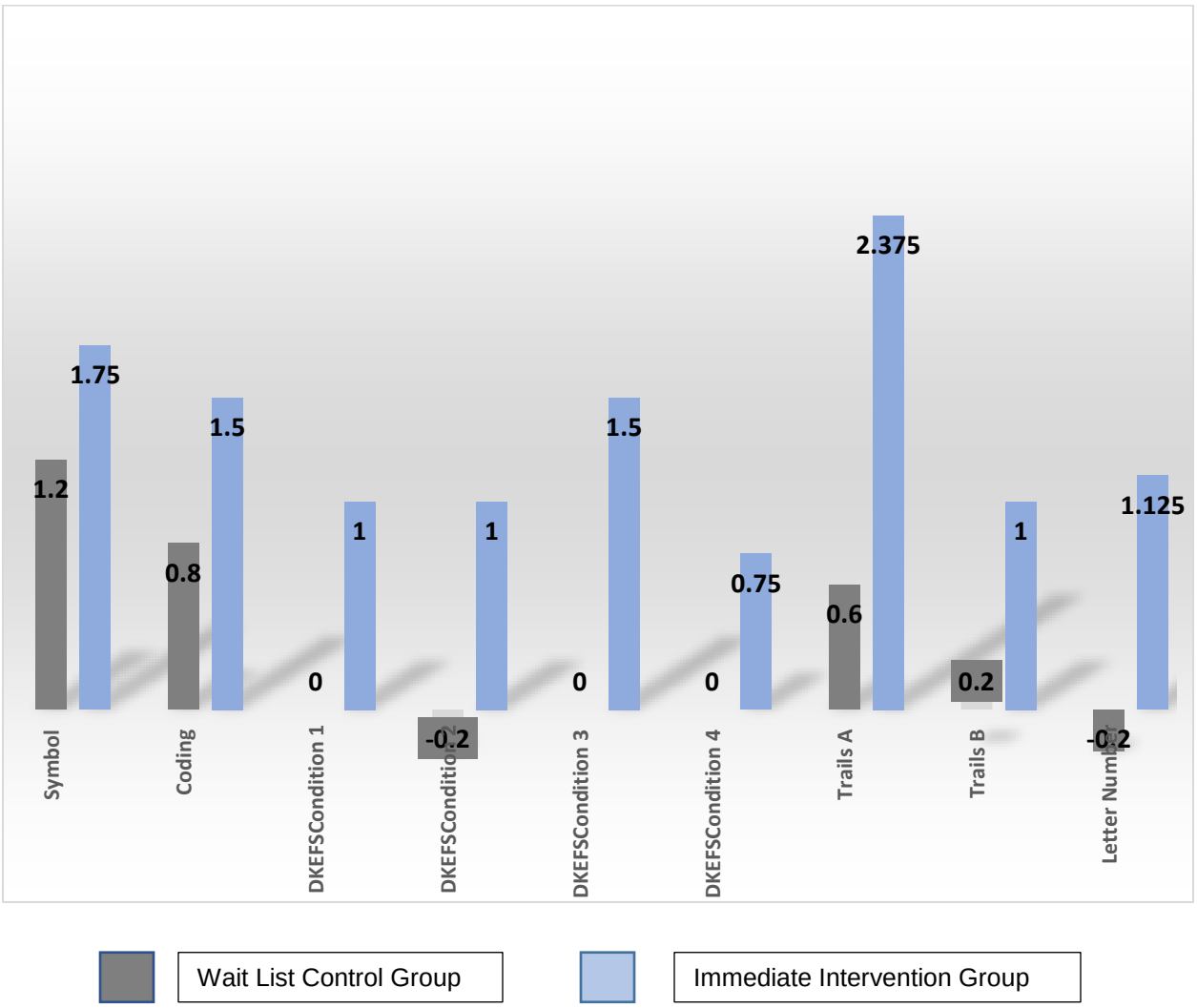


Table 1. Baseline Demographic Characteristics by Group

Demographic Characteristics	Group		Non-Parametric Analysis		
	Immediate Intervention (n=8)	Wait List Control (n=7)	Mann Whitney U	Z	P_{exact}
	Mean (SD)	Mean (SD)			
Age (years)	57.0 (5.56)	51.71 (6.9)	14.5	-1.569	.121
Education (years)	15.88 (2.17)	14.57 (2.5)	20.0	-0.987	.397
Months since final oncologic treatment	44.88 (7.26)	34.71 (9.27)	12.0	-1.860	.072
	Immediate Intervention (n=8) Count	**Wait List Control (n=7) Count**			
Race/Ethnicity					
Caucasian	8	4			
African American	0	2			
Hispanic	0	1			
Marital Status					
Never Married		1			
Married/Living with Partner	6	4			
Divorced	2	2			
Employment					
Full Time	5	4			
Part Time	2	1			
Retired		1			
Unemployed	1	1			

Table 2. Baseline Medical Characteristics by Group

Medical Characteristics	Group	
	Immediate Intervention (n=8) Count	Wait List Control (n=7) Count
Breast Cancer Stage		
Stage 0	1	
Stage 1 A	1	2
Stage II A	2	2
Stage II B	2	1
Stage III A	2	2
Tumor Type		
Infiltrating Ductal Carcinoma	4	6
Invasive Lobular Carcinoma	3	
Ductal Carcinoma In-situ	1	
Mixed Invasive Lobular and Ductal Carcinoma		1
Oncologic Treatment Type(s)		
Surgery + Chemotherapy + Radiation	4	4
Surgery+ Chemotherapy	2	
Surgery + Radiation	2	1
Surgery+ Chemotherapy +Pertuzumab		1
Surgery+ Chemotherapy+ Radiation + Pertuzumab		1
Menopause Type at Diagnosis		
Premenopausal	4	5
Postmenopausal	4	2
Current Hormone Therapy		
Aromatase Inhibitors	1	2
Selective Estrogen Receptor Modulators	5	1
No Hormone Therapy	2	4

Table 3. Baseline PROMIS® Symptom and FACT-Cog Self-Report Measures by Group

Self- Report Measures Baseline	Group		Non- Parametric Analysis		
	Immediate Intervention (n=8)	Wait List Control (n=7)	Mann Whitney U	Z	P_{exact}
PROMIS Short Form Symptom Measures	**T Score Mean (SD)**	**T Score Mean (SD)**			
Depression	46.08 (4.7)	42.66 (8.25)	18.0	-1.179	.281
Anxiety	49.88 (8.81)	44.87 (5.79)	18.5	-1.207	.281
Fatigue	49.09 (7.28)	44.53 (5.72)	28.0	0.000	1.000
Applied Cognition General Concerns	42.59 (8.87)	36.24 (6.86)	14.0	-1.622	.105
Applied Cognition Executive Function	37.39 (8.04)	43.59 (4.01)	15.0	-1.504	.132
Fact-Cog Version 3	**Subscale Score Mean (SD)**	**Subscale Score Mean (SD)**			
Perceived Cognitive Impairments (Cog PCI) Subscale	41.8 (17.25)	54.7 (13.95)	14.0	-1.622	.121
Impact of PCI on Quality of Life (CogQOL) Subscale	8.5 (4.38)	13.00 (2.77)	9.5	-2.154	.029
Comments from Others (CogOth) Subscale	12.88 (5.03)	14.86 (0.90)	23.5	-0.537	.613
Perceived Cognitive Abilities (CogPCA) Subscale	17.63 (7.07)	20.00 (7.30)	22.0	-0.696	.536

Table 4. Baseline Neuropsychological Test Mean (SD) and Non-Parametric Analysis by Group

Neuropsychological Test	Group				Non-Parametric Raw Score or Scaled Score Analysis		
	Immediate Intervention (n=8)		**Wait List Control Group** (n=7)				
	Raw Score (Word Count) Mean (SD)		**Raw Score (Word Count) Mean (SD)**		**Mann Whitney U**	**Z**	P_{exact}
Rey Auditory Verbal Learning							
Total Word Trials I-V Raw Score (# words out of 75)	57.13 (8.43)		49.86 (10.29)		15.0	-1.504	.152
Immediate Recall Raw Score (# words out of 15)	12.13 (3.14)		11.14 (3.24)		23.5	-0.525	.613
Delayed Recall Raw Score (# words out of 15)	12.25 (2.44)		11.71 (3.2)		25.5	-0.295	.779
Recognition Raw Score (# words out of 15)	14.38 (1.19)		14.00 (1.41)		23.0	-0.692	.613
	Scaled Score Mean (SD)	**Percentile**	**Scaled Score Mean (SD)**	**Percentile**			
WAIS IV Symbol Search	12.75 (4.17)	84	10.57 (5.56)	63	21.5	-0.756	.463
WAIS IV Coding	12.38 (3.46)	75	11.43 (4.50)	63	24.0	-0.468	.694
Delis Kaplan Executive Function							
Color Word Condition 1	11.00 (2.00)	63	9.57 (3.60)	50	21.0	-0.821	.463
Color Word Condition 2	10.63 (3.38)	56	8.86 (4.53)	37	20.5	-0.880	.397
Color Word Condition 3	11.75 (2.25)	71	11.14 (4.91)	63	27.0	-0.118	.955
Color Word Condition 4	12.63 (2.33)	80	10.86 (3.72)	63	20.0	-0.933	.397
Trails A	11.13 (2.03)	63	9.86 (3.13)	50	17.5	-1.228	.232
Trails B	11.75 (1.28)	71	10.86 (3.39)	63	18.5	-1.110	.281
WAIS IV Letter Number Sequencing	9.38 (0.74)	37	9.29 (1.70)	37	27.5	-0.059	.955

Table 5. Difference (Posttest Adjusted by Baseline) for PROMIS® T Scores, FACT-Cog Subscale Scores, and Non-Parametric Analysis by Group

PROMIS Short Form Surveys	Difference Scores		Non-Parametric Raw Sco or Scaled Score Analysis		
	Immediate Intervention (n=8)	**Wait List Control Group** (n=5)			
	T Score Difference Mean (SD)	**T Score Difference Mean (SD)**	**Mann Whitney U**	**Z**	***P exact***
Depression	-2.85 (4.37)	1.04 (5.91)	12.0	-1.189	.284
Anxiety	1.43 (5.77)	-1.76 (3.94)	14.0	-.956	.435
Fatigue	-4.30 (3.56)	-2.22 (3.17)	12.0	-1.171	.284
Applied Cognition General Concerns	-6.54 (5.70)	1.06 (3.24)	5.0	-2.196	.030
Applied Cognition Executive Function	10.08 (4.07)	1.26 (6.06)	4.0	-2.34	.019
Fact-Cog Version 3	**Subscale Score Difference Mean (SD)**	**Subscale Score Difference Mean (SD)**			
Perceived Cognitive Impairments (Cog PCI) Subscale	18.75 (10.22)	2.2 (11.88)	5.0	-2.202	.030
Impact of PCI on Quality of Life (CogQOL) Subscale	4.63 (2.33)	1.4 (1.67)	4.5	-2.291	.022
Comments from Others (CogOth) Subscale	2.25 (3.65)	0.80 (0.84)	15.5	-0.692	.524
Perceived Cognitive Abilities (CogPCA) Subscale	9.0 (5.81)	-2.8 (4.32)	3.5	-2.422	.011

Table 6. Difference (Posttest Adjusted by Baseline) Neuropsychological Tests and Non-Parametric Analysis by Group

Neuropsychological Test	Difference Scores		Non-Parametric Raw Score or Scaled Score Analysis		
	Immediate Intervention (n=8)	**Wait List Control Group** (n=5)			
	Difference Raw Score (Word Count) Mean (SD)	**Difference Raw Score (Word Count) Mean (SD)**	**Mann Whitney U**	**Z**	***p***
Rey Auditory Verbal Learning Test					
Total Word Trials I-V Raw Score (# words out of 75)	8.38 (7.27)	9.60	15.0	-.735	.462
Immediate Recall Raw Score (# words out of 15)	2.00 (2.67)	0.60	15.0	-.757	.449
Delayed Recall Raw Score (# words out of 15)	1.50 (1.77)	0.80	16.0	-.595	.552
Recognition Raw Score (# words out of 15)	0.63 (1.19)	0.80	18.0	-.361	.718
	Difference Scaled Score Mean (SD)	**Difference Scaled Score Mean (SD)**			
WAIS IV Symbol Search	1.75 (1.98)	1.20(4.09)	15.0	-0.755	.450
WAIS IV Coding	1.50 (2.00)	0.80 (1.30)	12.5	-1.138	.255
Delis Kaplan Executive Function					
Color Word Condition 1	1.00 (1.31)	0.00 (0.71)	9.5	-1.668	.095
Color Word Condition 2	1.00 (2.34)	-0.20 ((0.84)	11.5	-1.307	.191
Color Word Condition 3	1.50 (1.60)	0.00 (1.00)	9.5	-1.586	.113
Color Word Condition 4	0.75 (1.58)	0.00 (0.00)	15.0	-0.800	.424
Trails A	2.38 (2.45)	0.60 (1.52)	11.0	-1.336	.182
Trails B	1.00 (2.51)	0.20 (1.30)	17.0	-0.447	.655
WAIS IV Letter Number Sequencing	1.13 (2.80)	-0.20 ((0.84)	12.5	-1.256	.209

58

References

1. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Feb 20 2016;34(6):611-635.
2. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer. Jun 1 2004;100(11):2292-2299.
3. Hurria A, Goldfarb S, Rosen C, et al. Effect of adjuvant breast cancer chemotherapy on cognitive function from the older patient's perspective. Breast cancer research and treatment. Aug 2006;98(3):343-348.
4. Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. Neuropsychology review. Jun 2008;18(2):121-131.
5. Jenkins V, Shilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. British journal of cancer. Mar 27, 2006;94(6):828-834.
6. Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Jan 15, 2002;20(2):485-493.
7. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Oct 10, 2010;28(29):4434-4440.
8. Bender CM, Sereika SM, Berga SL, et al. Cognitive impairment associated with adjuvant therapy in breast cancer. Psycho-oncology. May 2006;15(5):422-430.
9. McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast cancer research and treatment. Oct 2010;123(3):819-828.
10. McDonald BC, Conroy SK, Smith DJ, West JD, Saykin AJ. Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. Brain, behavior, and immunity. Mar 2013;30 Suppl: S117-125.
11. Conroy SK, McDonald BC, Smith DJ, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast cancer research and treatment. Jan 2013;137(2):493-502.
12. Ferguson RJ, McDonald BC, Saykin AJ, Ahles TA. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Sep 1 2007;25(25):3866-3870.
13. Cull A, Hay C, Love SB, Mackie M, Smets E, Stewart M. What do cancer patients mean when they complain of concentration and memory problems? British journal of cancer. Nov 1996;74(10):1674-1679.
14. Mulrooney T. Cognitive impairment after breast cancer treatment. Clinical journal of oncology nursing. Aug 2008;12(4):678-680.
15. Myers JS. Chemotherapy-related cognitive impairment: the breast cancer experience. Oncology nursing forum. Jan 2012;39(1): E31-40.
16. Kanaskie ML, Loeb SJ. The experience of cognitive change in women with breast cancer following chemotherapy. Journal of cancer survivorship: research and practice. Oct 25, 2014.
17. Brezden CB, Phillips KA, Abdolell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Jul 2000;18(14):2695-2701.
18. Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. Journal of clinical and experimental neuropsychology. Oct 2004;26(7):955-969.
19. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer. Feb 1, 1999;85(3):640-650.

20. Schagen SB, Muller MJ, Boogerd W, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Sep 2002;13(9):1387-1397.
21. van Dam FS, Schagen SB, Muller MJ, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. Journal of the National Cancer Institute. Feb 4, 1998;90(3):210-218.
22. Shilling V, Jenkins V, Morris R, Deutsch G, Bloomfield D. The effects of adjuvant chemotherapy on cognition in women with breast cancer--preliminary results of an observational longitudinal study. Breast (Edinburgh, Scotland). Apr 2005;14(2):142-150.
23. Stewart A, Collins B, Mackenzie J, Tomiak E, Verma S, Bielajew C. The cognitive effects of adjuvant chemotherapy in early stage breast cancer: a prospective study. Psycho-oncology. Feb 2008;17(2):122-130.
24. Tager FA, McKinley PS, Schnabel FR, et al. The cognitive effects of chemotherapy in post-menopausal breast cancer patients: a controlled longitudinal study. Breast cancer research and treatment. Aug 2010;123(1):25-34.
25. Correa DD, Ahles TA. Neurocognitive changes in cancer survivors. Cancer journal (Sudbury, Mass.). Nov-Dec 2008;14(6):396-400.
26. Baddeley A. Working Memory. New York: Oxford University Press, Inc.; 1986.
27. Bartlett SJ, Orbai AM, Duncan T, et al. Reliability and Validity of Selected PROMIS Measures in People with Rheumatoid Arthritis. PloS one. 2015;10(9): e0138543.
28. Choi SW, Schalet B, Cook KF, Cella D. Establishing a common metric for depressive symptoms: linking the BDI-II, CES-D, and PHQ-9 to PROMIS depression. Psychological assessment. Jun 2014;26(2):513-527.
29. Cella D, Schalet, B., Kallen, M., Lai, Jin-Shei, Cook, K., Rutsohn, J., Choi, S. PROsetta Stone Analysis Report: A Rosetta Stone for Patinet Reported Outcomes. September 15, 2016 2016; 2:1-229.
30. Cheung YT, Lim SR, Shwe M, Tan YP, Chan A. Psychometric properties and measurement equivalence of the English and Chinese versions of the functional assessment of cancer therapy-cognitive in Asian patients with breast cancer. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. Sep-Oct 2013;16(6):1001-1013.
31. Cullum C, Larrabee, G. WAIS-IV Use in Neuropsychological Assessment. In: Weiss L, Saklofske, DH, Coalson, DL, Raiford, SE, ed. WAIS-IV Clinical Use and Interpretation. Vol 1. First ed. London: Elsevier; 2010:283.
32. Dikmen SS, Heaton RK, Grant I, Temkin NR. Test-retest reliability and practice effects of expanded Halstead-Reitan Neuropsychological Test Battery. Journal of the International Neuropsychological Society: JINS. May 1999;5(4):346-356.
33. Lemay S, Bedard MA, Rouleau I, Tremblay PL. Practice effect and test-retest reliability of attentional and executive tests in middle-aged to elderly subjects. The Clinical neuropsychologist. May 2004;18(2):284-302.
34. Strauss E, Sherman, E., Spreen, O. A compendium of Neuropsychological Tests Administration, Norms, and Commentary. Third Edition ed. New York, New York: Oxford University Press; 2006.
35. van den Burg W, Kingma A. Performance of 225 Dutch school children on Rey's Auditory Verbal Learning Test (AVLT): parallel test-retest reliabilities with an interval of 3 months and normative data. Archives of clinical neuropsychology: the official journal of the National Academy of Neuropsychologists. Aug 1999;14(6):545-559.
36. Lundqvist A, Grundstrom K, Samuelsson K, Ronnberg J. Computerized training of working memory in a group of patients suffering from acquired brain injury. Brain injury: [BI]. 2010;24(10):1173-1183.
37. Pearson. Research Coaching Manual V2.0 Cognitive Memory Training. Upper Saddle River, NJ: NCS Pearson, Inc; 2014.
38. Chen X, He X, Tao L, et al. The Working Memory and Dorsolateral Prefrontal-Hippocampal Functional Connectivity Changes in Long-Term Survival Breast Cancer Patients Treated with Tamoxifen. The international journal of neuropsychopharmacology. May 01, 2017;20(5):374-382.
39. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. Jul 15, 2010;116(14):3348-3356.