PROTOCOL TITLE: Randomized, Controlled Trial of an Individualized Exercise Oncology Program for Newly Diagnosed Breast Cancer Patients

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	17JAN2020	Added new method of recruitment (Interest Flyer)	No

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1.0 Study Summary

Study Title	Randomized, Controlled Trial of an Individualized Exercise Oncology Program for Newly Diagnosed Breast Cancer Patients
Study Design	Randomized, controlled trial
Primary Objective	The primary objective is to test the effect of an individualized exercise oncology program on healthcare utilization, 30-day hospital readmission, pain, and cancer treatment tolerance.
Secondary Objective(s)	The secondary objective is to examine the feasibility of an individualized exercise oncology program via adherence and attrition rates.
Research Intervention(s)/ Investigational Agent(s)	Individualized Exercise Oncology Program
IND/IDE #	N/A
Study Population	Female patients age 18+ newly diagnosed with stage 0, 1 or 2 breast cancer.
Sample Size	70
Study Duration for individual participants	12 weeks
Study Specific Abbreviations/ Definitions	N/A

2.0 Objectives*

The primary objective is to test the effect of an individualized exercise oncology program on healthcare utilization, 30-day hospital readmission, pain, and cancer treatment tolerance.

> H1: Among women newly diagnosed with stage 0, 1 or 2 breast cancer, those enrolled in an individualized exercise oncology program will have fewer emergency room (ER) visits, fewer hospital encounters, fewer 30-day hospital readmissions, fewer breaks in cancer treatment, less pain, and better cancer treatment tolerance than those in the control group over 3 months.

The secondary objective is to examine the feasibility of an individualized exercise oncology program via adherence and attrition rates.

> H2: Among women newly diagnosed with stage 0, 1 or 2 breast cancer and enrolled in an individualized exercise oncology program, adherence to scheduled exercise sessions will average 70% or more, and program attrition will average 70% or less over 3 months.

3.0 Background*

In 2018, it was estimated that there were 1.7 million new cancer diagnoses in the U.S.[1] For all types of cancer, mortality rates are on the decline[1], and patients are living longer with the chronic and late effects of treatment. This often results in costly hospital readmissions and emergency department (ED) visits, leading to increased costs, lowered health outcomes, and lengthened stays for patients.[2]

Several meta-analyses report that exercise interventions are beneficial for patients undergoing cancer treatment, in that they reduce symptom severity[3] and improve cancer-related fatigue[4-6], cardiac function[7], muscle weakness[8], and overall quality of life[9]. Yet, it still remains that less than 5% of patients are ever referred to an exercise oncology program during treatment[10]. Therefore, economic evaluations of exercise oncology are warranted, in attempt to evaluate the integration of exercise oncology as a standard part of clinical practice.

Maple Tree Cancer Alliance[11] has developed an oncology exercise program, which results in improved health outcomes, and also cost-saving for facilities and payers. Our retrospective data demonstrated that individualized exercise during cancer treatment significantly reduced ED visits, 30-day readmissions, and length of hospital stays[12] resulting in a payer benefit of $3,000/patient over the first 6 months of enrollment into the Maple Tree Exercise Oncology program[2]. As a follow up to this research, the purpose of the present study is to prospectively analyze the cost savings of an individualized exercise oncology program when under a rigorous, randomized, controlled design. We hypothesize that

individualized exercise training during cancer treatment will improve treatment outcome, lending to a decrease in healthcare-related expenditure.

4.0 Study Endpoints*

Primary Study Endpoints:

- Total number of missed fractions, determined via EMR
- A break in cancer treatment, defined as missing ≥3 fractions due to patient condition, determined via EMR
- ER visits, as determined via EMR
- Inpatient and outpatient hospital encounters, as determined via EMR
- Hospital readmission for the same presenting issue, as determined via EMR
- Hospital length of stay (if hospitalized), as determined via EMR
- Cancer treatment adherence, determined via EMR
- Medications for cancer treatment symptom management, determined via EMR
- Cancer treatment-related side effects, determined via EMR
- Patient-rated pain measured by visual analog scale, as determined via EMR
- Cancer treatment tolerance, measured by the Eastern Cooperative Oncology Group (ECOG) Performance Status score, as determined via EMR
- Quality of Life, as measured by the McGill Quality of Life Measure, administered in-person at weeks 1 and 12 (http://www.npcrc.org/files/news/mcgill_quality_of_life.pdf)

Secondary Study Endpoints:

- Exercise session adherence rate among the Exercise Group, collected from the Maple Tree Cancer Alliance participant records.
- Exercise program attrition rate among the Exercise Group, collected from the Maple Tree Cancer Alliance participant records.

Safety endpoints are:

- Objective worsening lymphedema due to physical activity, as determined by treating oncologist
- Pathologic fracture
- Recommendation to stop physical activity by treating oncologist

Demographic and Baseline Clinical Characteristics:

- Age, as determined via electronic medical record (EMR)
- Diagnosis and diagnostic stage, as determined via EMR
- Diagnosis Date, as determined via EMR
- Body mass index, as determined by height and weight in EMR
- Comorbid chronic conditions (hypertension, diabetes, COPD), as determined via EMR
- Race/ethnicity, as determined via EMR

5.0 Study Intervention/Investigational Agent

Exercise Group

The study intervention is a supervised, individualized exercise oncology program described in previous literature[2,3,12] and provided by Maple Tree Cancer Alliance, a non-profit organization providing exercise training to individuals with cancer (https://www.mapletreecanceralliance.org/). This organization was founded in 2011 and currently operates in 9 hospitals serving Ohio and Pennsylvania, offering free exercise programs and nutritional guidance to approximately 500 patients annually to help relieve side effects related to cancer treatment.

Patients in the supervised, individualized exercise oncology program (Exercise Group) will complete a 60-minute exercise session once per week for 12 weeks at Maple Tree Cancer Alliance. The exercise sessions will be individualized to the patient's needs and fitness level by a trainer with a bachelor's degree in exercise science and a national certification for exercise oncology. A patient will work with the same trainer throughout the study, who will plan the patient's individualized exercise regimen, and who will provide one-on-one supervision for the duration of each 60-minute session. Each 60-minute session will include cardiovascular, strength, and flexibility training. Cardiovascular exercise will be performed on a treadmill. The intensity level for the aerobic exercise ranges from 30-45% of the individual's predicted VO_{2max}, controlled by heart monitors (model S810i; Polar Electro) and lasting 30 min. Strength training will involve a full body workout, with emphasis on all major muscle groups and employing machines, free weights, and resistance tubing. Patients will complete 3 sets of 10 repetitions for each strength exercise. Flexibility training will involve static stretching of all major muscle groups for 15-20 seconds at the completion of each workout.

Control Group

The control group will receive the current standard of care, which includes a resource guide with various options available to the cancer survivor. Within this guide are tips for healthy eating and pictures of standard exercises to improve fitness.

6.0 Procedures Involved*

The study design is an open-label, randomized, controlled, parallel-group trial. Women age 30-80 with a recent diagnosis of stage 0, 1 or 2 breast cancer who meet inclusion and exclusion criteria will be invited to participate. As is typical and customary, a diagnosis within the last 12 weeks will be considered a recent diagnosis. Upon study enrollment and informed consent, patients will be randomly assigned to the Exercise Group or the Control Group. Random assignment will be conducted in blocks of 10 to ensure equal groups (See Appendix A). Participants will be enrolled in the study for 12 weeks.

7.0 Data and Specimen Banking*

N/A

8.0 Sharing of Results with Subjects*

Most study parameters come from the EMR; patients have ready access to these data. The information collected outside the EMR includes quality of life (all patients) and exercise session adherence rate (Exercise Group). The Exercise Group will also receive reports on their cardiovascular, strength, and flexibility assessments.

9.0 Study Timelines*

Patient recruitment will begin after IRB approval is obtained. Each patient will be enrolled in the study for 12 weeks. Study enrollment is expected to take place over approximately 6 months, until 70 patients are enrolled. When 70 patients have been enrolled, enrollment will close, and active subjects will be followed for the remainder of their 12 week participation. Once all patients have completed the study, data will be abstracted from the EMR and analyzed within 12 months.

10.0 Inclusion and Exclusion Criteria*

Patients will be selected according to the Consolidated Standard of Reporting Trials criteria. Criteria not determined via EMR are determined via the form in Appendix B. Inclusion criteria are:

- Female; determined from electronic medical record
- Initial stage 0, 1 or 2 breast cancer diagnosis within the past 12 weeks determined from electronic medical record
- Age 30-80; determined from electronic medical record
- Physician clearance to participate in exercise

Exclusion criteria are:

- Participation in supervised physical exercise within 6 months prior to study enrollment
- Currently pregnant or planning to become pregnant
- Non-English speaking
- Unable to make own medical decisions and/or to follow verbal instructions

11.0 Vulnerable Populations*

N/A

12.0 Local Number of Subjects

A total of 70 subjects will be enrolled (35 in each study group). This sample size provides 80% power to detect a medium effect size in number of missed treatment fractions between study groups. Only subjects who meet eligibility criteria will be enrolled.

13.0 Recruitment Methods

13.1 Eligible patients will be contacted in person when they are at KMC or Soin MC for regular appointments. If in-person appointments are not convenient times, patients may be contacted by phone by the research coordinator.

13.2 The research coordinator will attend breast tumor conferences to identify eligible patients and seek physician approval to approach the patients about study participation.

13.3 *A printed Interest Form will be provided to patients in their initial Breast Cancer Journey packets and during the Breast Cancer Class.*

13.4 The subjects will not receive compensation for their participation in the study.

14.0 Withdrawal of Subjects*

Any study patient who experiences a safety endpoint under section 4.0, including recommendation to stop physical activity by treating oncologist, will be withdrawn from the study. Final, non-physical activity measures will be collected on patients who are withdrawn.

As Maple Tree provides free services to patients undergoing cancer treatment, a patient withdrawn from the study for safety reasons could, at a later date and when it is deemed safe by her physician, again receive exercise services at Maple Tree (outside the study context).

15.0 Risks to Subjects*

The risks associated with the study intervention are commensurate with light to moderate physical activity, such as muscle soreness. Given the low-impact nature of the exercise and the one-on-one supervision during exercise sessions, the risk of injury or another adverse outcome is very low. Participants in the Exercise Group will have an exercise program individualized to their needs and physical abilities, and participants will be closely monitored during exercise sessions. The

study will not be blinded; patients and treating physicians will be aware of group status and if the treating oncologist recommends the subject stop physical activity, the subject will be withdrawn from the study.

The Exercise Group may incur some travel costs to attend exercise sessions.

No psychological, social, or legal risks are anticipated.

16.0 Potential Benefits to Subjects*

Participants in the exercise intervention may experience reduced pain and relief from other effects of cancer treatment, thus reducing breaks in treatment and hospital or ER visits. Participants may also experience improved energy and mood and may establish a positive behavioral pattern of physical activity that will extend beyond the study.

17.0 Data Management* and Confidentiality

Data Management:
All study parameters from the EMR will be downloaded by an EMR specialist via a report, de-identified, and housed in a Microsoft Excel database. Patient forms, including consent forms, will be stored in a locked file cabinet at Maple Tree Cancer Alliance. All patients will be assigned a Study ID number and a list linking patient names to Study ID number will be kept separately from the study data, on a password-protected computer. Data from patient forms will be entered into the master Microsoft Excel spreadsheet. Only Study ID will be used to identify patients in the spreadsheet.

Data Analysis Plan:
Data will be analyzed using IBM SPSS Statistics version 25.0. Continuous variables will be described using mean, median, standard deviation, and range. Nominal variables will be described using frequency and percentage.

Baseline demographic and clinical characteristics will be compared between treatment and control groups to establish equivalence; any statistically significant differences between study groups will be controlled statistically. Continuous endpoints will be tested for normality using Shapiro-Wilk tests. Differences between study groups on continuous endpoints will be evaluated using independent samples *t*-tests for normally distributed endpoints and Mann-Whitney *U* tests for non-normally distributed endpoints. Nominal endpoints will be compared between groups using chi-square tests. Alpha will be set to .05, two-tailed for all tests.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

N/A; The probability of harm or discomfort anticipated in this study are no greater than those encountered in daily life or during the performance of routine physical or psychological tests.

19.0 Provisions to Protect the Privacy Interests of Subjects

Subject identifiers will only be included in the master list linking subjects to their Study ID (Appendix C). Subjects in the Control Group will receive standard care, including usual privacy standards. Subjects in the Exercise Group will interact with the same trainer throughout the study, so that rapport can be developed, putting the subject at ease. All exercise activities will be individually tailored to the subject's needs.
To access data from the subjects' electronic medical records, a request will be sent to Information Systems (IS). Once received, identifiers will be replaced with Study ID number.

20.0 Compensation for Research-Related Injury

N/A; The study does not involve more than minimal risk.

21.0 Economic Burden to Subjects

Subjects in the Exercise Group may incur costs associated with once weekly travel to Maple Tree Cancer Alliance. No other study-related costs to subjects are expected.

22.0 Consent Process

All patients will be fully informed about the study and will have time to ask questions and consider their decision to participate. A research intern for Maple Tree Cancer Alliance, Kara Gnau, will provide a written informed consent form to eligible patients and meet with them in person to discuss the study in a private room at the Kettering Cancer Center or the Soin Cancer Center. Patients will be provided with the informed consent form and the intern will go through the information in the form with the patient. Patients will be invited to take the form home and talk with family and friends before deciding if they would like to participate. If patients wish to take some time to make the decision, they may inform the intern about their decision to participate or decline participation via phone.

23.0 Process to Document Consent in Writing

Participants will document consent to participate using the consent form in Appendix D.

24.0 Setting

Subjects will be recruited from patient populations at Kettering and Soin Cancer Centers and identified through presentation at breast tumor conferences held at these facilities (see Section 13.0). For the Exercise Group, exercise will occur at Maple Tree Cancer

Alliance as described in Section 5.0. For the Control Group, all research activities will entail usual care at standard treatment locations. Treatment decisions for both groups are independent of study participation.

25.0 Resources Available

The study team has adequate resources to execute this study in a timely manner.

26.0 Multi-Site Research*

Not applicable.

References

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8. Wonders, KY, Jennings, J, & Smith, K. A comprehensive cancer care plan: Examining the role of exercise, nutrition, and emotional support in cancer recovery. *Journal of Palliative Care and Medicine*; 2012;S1:003
9. Huether K, Abbott L, Cullen L, Cullen L, Gaarde A. Energy through motion: an evidence-based exercise program to reduce cancer-related fatigue and improve quality of life. Clinical Journal Of Oncology Nursing. 2016;20(3), E60-E70.
10. Smith SR, Zheng JY. The Intersection of Oncology Prognosis and Cancer Rehabilitation. Curr Phys Med Rehabil Rep. 2017;5:46-54.
11. See https://www.mapletreecanceralliance.org/
12. Wonders, K. (2018). Supervised, Individualized Exercise Programs Help Mitigate Costs during Cancer Treatment. J Palliat Care Med 8:338.

Appendix A: Randomization Scheme using Block Size of 10

Subject	Study Group Assignment
1	Control
2	Exercise
3	Exercise
4	Exercise
5	Control
6	Control
7	Control
8	Control
9	Exercise
10	Exercise
11	Exercise
12	Control
13	Control
14	Control
15	Exercise
16	Exercise
17	Control
18	Control
19	Exercise
20	Exercise
21	Control
22	Exercise
23	Exercise
24	Control
25	Exercise
26	Exercise
27	Control
28	Control
29	Exercise
30	Control
31	Exercise
32	Exercise
33	Control
34	Control
35	Exercise
36	Control
37	Control
38	Exercise
39	Exercise
40	Control
41	Exercise
42	Control

43	Exercise
44	Exercise
45	Exercise
46	Control
47	Control
48	Exercise
49	Control
50	Control
51	Exercise
52	Exercise
53	Exercise
54	Control
55	Control
56	Control
57	Control
58	Exercise
59	Exercise
60	Control
61	Control
62	Control
63	Exercise
64	Exercise
65	Control
66	Exercise
67	Control
68	Exercise
69	Exercise
70	Control

Appendix B

Randomized, Controlled Trial of an Individualized Exercise Oncology Program

Determination of eligibility (to be completed by Maple Tree Cancer Alliance research intern)

Patient Name _____

Is the patient female, as determined from electronic medical record?	□ Yes □ No (Ineligible)
Does the patient have an initial stage 1 or 2 breast cancer diagnosis within the past 12 weeks, determined from electronic medical record?	□ Yes □ No (Ineligible)
Is the patient age 30-80, determined from electronic medical record?	□ Yes □ No (Ineligible)
Does the patient have documented physician clearance to participate in exercise?	□ Yes □ No (Ineligible)
Has the patient participated in supervised physical exercise within the past 6 months?	□ Yes (Ineligible) □ No
Is the patient currently pregnant or planning to become pregnant?	□ Yes (Ineligible) □ No
Does the patient speak and read English fluently?	□ Yes □ No (Ineligible)
Is the patient able to make their own medical decisions and to follow verbal instructions?	□ Yes □ No (Ineligible)

Appendix C: Master list linking patients to Study ID and documenting study participation for CONSORT reporting

Patient Last Name	Patient First Name	Date Assessed for Eligibility (mm/dd/yyyy)	Excluded? (Y/N)	If Excluded, reason (did not meet eligibility criteria, declined to participate, other)	Study ID (N/A for those excluded)	Random Assignment (Exercise Group, Control Group)
					1	
					2	
					3	
					4	
					5	
					6	
					7	
					8	
					9	
					10	
					etc.	