Coversheet

Study Title: Feasibility of using remotely-delivered metacognitive strategy training to address cancer-related cognitive impairment in breast cancer

Institution: University of Missouri

NCT Number: NCT05505045

IRB Number: 2066383

Consent approval date: November 15, 2022

Protocol and Statistical Analysis Plan approval date: January 9, 2023

Written Consent to Participate in a Research Study

Project Title: Feasibility of using remotely-delivered metacognitive strategy training to address cancer-related cognitive impairment in breast cancer
Principal Investigator Name: Anna E. Boone, PhD, MSOT, OTR/L
IRB Assigned Project Number: 2066383

Key Information About the Study

You are being asked to participate in a research study. The purpose of the research study is to evaluate the feasibility and preliminary effect of metacognitive strategy training delivered via telehealth methods to improve activity performance, cognition, and quality of life in breast cancer survivors. You are being asked to participate in 10 occupational therapy intervention sessions through videoconferencing. You are also being asked to complete an assessment battery before the intervention and after the intervention. Possible benefits include improvements from either participating in either the problem-solving intervention (described below) or from the attention control intervention by performing goal-related everyday life activities better and/or experiencing less CRCI-related impairment. Some possible risks may include: (1) a breach of confidentiality where identifiable health information related to the participants is inadvertently made available to individuals beyond the research team; (2) psychological distress while discussing changes in your abilities following cancer treatment; or (3) physical injury. Participants will be encouraged to perform their chosen activity-related goals at home. Some of these goals involve physical activity, (e.g., cooking), in which the participant could sustain a physical injury such as a cut on the hand. These activities will all be common everyday life activities that the participant is already doing at home.

Please read this form carefully and take your time. Let us know if you have any questions before participating. The research team can explain words or information that you do not understand. Research is voluntary and you can choose not to participate. If you do not want to participate or choose to start then stop later, there will be no penalty or loss of benefits to which you are otherwise entitled.

Purpose of the Research

You are being asked to participate in this study because you are female with a history of breast cancer and chemotherapy treatment within the past three years. The purpose of the study is to evaluate the practicality and effect of a structured, problem-solving intervention delivered via telehealth methods to improve activity performance, cognition, and quality of life.

What will happen during the study?

You are being be asked to complete the following activities:

- **Pre-intervention assessments** for approximately 2.5 hours that will consist of questionnaires, interviews, and thinking tests.

IRB Approval Date: Nov 15, 2022; Written Consent Form ID #620580; Amendment ID #382005

- **10, 45-60 minute intervention sessions** delivered via videoconferencing. These will either consist of the problem-solving intervention or educational resources provided in 10, 45-60 minute intervention sessions.
- **Post-intervention sessions:** for approximately 2 hours that will consist of questionnaires, interviews, and thinking tests.

Your participation is expected to last a total of 12 weeks.

There will be about 38 subjects participating in this study.

What are the expected benefits of the study?

You may or may not benefit as a result of your participation in the study. Information learned from the study may help other people in the future. You may potentially experience improvement in your ability to perform everyday life activities better and/or experience less cancer-related cognitive impairment.

What are the possible risks of participating in this study?

There are minimal risks expected when taking part in this study. There are some that we know about and some may not know about yet. Some possible risks include (1) a breach of confidentiality where identifiable health information related to the participants is inadvertently made available to individuals beyond the research team; (2) psychological distress while discussing changes in your abilities following cancer treatment; or (3) physical injury.

To help lower these possible risks, we will keep your information in a password protected file on a secure network that has restricted access. All data will be obtained by the study team will be for research purposes only and will be de-identified prior to data entry into our secure electronic database. Any hard copy data will be locked in filing cabinets in the private offices of the PI. All electronic data will be maintained on one web-based, secure, centralized database. The database will use the REDCap® platform and can only be accessed through two password protected portals. All data entered into the REDCap® database will be stored on University of Missouri secure servers and will have access restricted to only members of the research team. In the rare event participants experience psychological distress when answering questions during assessments, they will be reminded that they can decline to answer any questions that may make them uncomfortable and that participation is completely voluntary.

We will tell you about any new important information we learn that may affect your decision to continue to participate in this study.

What other choices do I have if I don't want to be in this study?

You are not required to be in this study. You can simply choose not to participate. You can look for other research projects you may be interested in instead of this study.

Will I receive compensation for taking part in this study?

IRB Approval Date: Nov 15, 2022; Written Consent Form ID #620580; Amendment ID #382005

You will be compensated for taking part in this study. For your time and effort, you will receive $75 via check payment within one month of your pre-assessments and post-assessments for a total of $150.

Are there any costs for participating in this study?

You should not expect any additional costs by participating in this study.

Other costs to you from being in this study may include transportation, parking, childcare, and/or time off work.

You should discuss any questions about costs with the researchers before agreeing to participate.

Will information about me be kept private?

The research team is committed to respecting your privacy and keeping your personal information confidential. We will make every effort to protect your information to the extent allowed by law. Your records will be given a code number and will not contain your name or other information that could identify you. The code number that connects your name to your information will be kept in a separate, secure location.

When the results of this research are shared, we will remove all identifying information so it will not be known who provided the information. Your information will be kept as secure as possible to prevent your identity from being disclosed.

We may share what we collected from you as part of this research, after removing your identifiers, for future research without additional informed consent from you.

Who do I contact if I have questions or concerns?

If you have questions about this study or experience a research-related injury, you can contact the University of Missouri researcher at (573) 882-7023 or booneae@umsystem.edu.
If you have questions about your rights as a research participant, please contact the University of Missouri Institutional Review Board (IRB) at 573-882-3181 or muresearchirb@missouri.edu. The IRB is a group of people who review research studies to make sure the rights and welfare of participants are protected.

If you want to talk privately about any concerns or issues related to your participation, you may contact the Research Participant Advocacy at 888-280-5002 (a free call) or email muresearchrpa@missouri.edu.

Do I get a copy of this consent?

You will receive a copy of this consent for your records.
We appreciate your consideration to participate in this study.

IRB Approval Date: Nov 15, 2022; Written Consent Form ID #620580; Amendment ID #382005

Consent Signatures

Subject's Signature	**Date**

IRB Approval Date: Nov 15, 2022; Written Consent Form ID #620580; Amendment ID #382005

SOCIAL/BEHAVIORAL/EDUCATIONAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: Feasibility of using remotely-delivered metacognitive strategy training to address cancer-related cognitive impairment in breast cancer
IRB Number: 2066383
Version Number: 4
Version Date: January 9, 2023
Principal Investigator: Anna E. Boone, PhD
Funding Source: National Institute of Child Health and Human Development

I. Research Objectives/Background

1. The goal of this proposed project is to evaluate the feasibility and preliminary effect of metacognitive strategy training delivered via telehealth methods to improve activity performance, cognition, and quality of life in breast cancer survivors.
2. Breast cancer survivors often self-report cognitive changes after treatment for cancer (e.g. cancer-related cognitive impairment (CRCI)). These cognitive changes have a devastating impact on everyday life activities. Rehabilitation of CRCI faces two primary barriers including access to rehabilitation services and limited knowledge of what effective CRCI approaches are. In other conditions, such as traumatic brain injury and stroke, metacognitive strategy training (MCST) is a practice standard to address cognitive impairment. The Cognitive-Orientation to daily Occupational Performance (CO-OP) approach is a MCST intervention in which subjects are taught a general cognitive strategy that can be applied in known and novel contexts to devise task specific strategies to engage in an activity. Our preliminary data suggest that CO-OP may have a positive impact on activity performance, subjective and objective cognition, and quality of life in breast cancer survivors with CRCI. While current evidence supports the remote delivery of strategy-based interventions like CO-OP, this intervention has not been evaluated in breast cancer survivors with CRCI.

II. Recruitment Process

1. All subjects will have had a breast cancer diagnosis. We will recruit participants who have been seen for cancer treatment at Ellis-Fischel (EF) Cancer Center at the University of Missouri or will be recruited from the community. All patients seen at EF for cancer treatment will be available for recruitment for this study through the medical and rehabilitation oncology team at EF. A recruitment flyer will be used to recruit individuals from the community. We will share our study flyer and information about our study with various cancer organizations and support groups so that they can advertise our study on their websites, on their social media, or in their newsletters.

2. The medical and rehabilitation team at EF will identify potential subjects from the registry based on the following inclusion/exclusion criteria of this study (see complete list

below): (1) age, (2) time post-treatment; (3) cancer diagnosis; and (4) other neurological diagnoses. Contact information for potential subjects will be forwarded to the research team for this study on a weekly basis. Potential subjects will be contacted over the phone by a research coordinator to determine interest in this study. Interested potential subjects will complete a prescreening survey to further establish eligibility: (1) CFQ; (2) ability to read, write, and speak English. After completion of the prescreening survey, the research coordinator will arrange a time to obtain electronic written informed consent and to complete the screening/baseline assessment emotely via Zoom teleconferencing platform.

III. Consent Process

1. Potential participants who are scheduled for a baseline assessment will be mailed a copy of the consent form and be sent an electronic version. The consent form will be mailed or e-mailed prior to the baseline testing session to allow sufficient time for review. On the first session via videoconferencing the research coordinator or research assistant will explain the informed consent process to the potential participant. The specific details on the informed consent form will be reviewed. In particular, the person will be told the procedures she will participate in, the potential risks and benefits of participation, and her right to refuse participation at any time without any effect on her subsequent health care. The person then will be given another opportunity to read the consent form. After reading it, the study team member will answer any specific questions, highlight the important details of the study again, and remind the person of her rights as a participant. The person will then be asked to show a photo ID to verify identity and then electronically sign the consent form. A copy of the form and a brochure explaining the person's rights under the HIPAA regulations will be given to the person for her records. The signed consent form then will be signed by the person administering consent. The electronic consent form will be filed on a secure server and will only be accessible by a few members of the research team.

IV. Inclusion/Exclusion Criteria

- Inclusion Criteria:
  •Women aged 40-80years old
  •self-reported CRCI (Cognitive Failures Questionnaire (CFQ) score >30)
  •completed full course of chemotherapy at least 6 months, but no later than 3 years, prior to participation
  •able to read, write, and speak English fluently
  •able to provide valid informed consent
  •have a life expectancy of greater than 6 months at time of enrollment
  •diagnosed with breast cancer (invasive ductal or lobular BrCA Stages I, II, or III) and completed chemotherapy within the preceding three years
  •on stable doses of medications (i.e., no changes in past 60 days)

Exclusion Criteria:
•prior cancer diagnoses of other sites with evidence of active disease within the past year

•active diagnoses of any acute or chronic brain-related neurological conditions that can alter normal brain function (e.g., Parkinson's disease, dementia, cerebral infarcts, traumatic brain injury)
•severe depressive symptoms (Personal Health Questionnaire (PHQ-9) score of ≥21)

- The screening methods identified in parentheses next to appropriate inclusion/exclusion criteria will be used to verify appropriate selection of study participants.

V. Number of Subjects

1. We will enroll approximately 44 (final sample of 38 human subjects) for this single-blind, parallel, randomized clinical trial.
2. The purpose of this R03 is to obtain estimates of effect and precision of response in 38subjects (19/group) so that a more formal sample size calculation can accompany our future NIH R01 application. A total sample size of 44will be recruited to allow for 15% attrition. Sample size estimations are based on two primary outcome measures: the Canadian Occupational Performance Measure (COPM) and the NeuroQoL Cognitive Function Short Form. We have estimated this sample size based upon preliminary data, published performance data of the breast cancer population,55and theminimal clinically important difference (MCID) for the outcome measures specified56-58(Table 1). While we will not complete hypothesis testing, we usedthe following assumptions of hypothesis testing to estimate our sample: (1) power of 0.80; (2) a 2-tailed alpha of .05; and (3) an estimated attrition rate of 15% based on the pilot study.

VI. Study Procedures/Study Design

1. This is a single-blind, parallel, exploratory, randomized controlled trial to further evaluate the feasibility and the effect of remote delivery of CO-OP on CRCI in breast cancer survivors. Individuals from the community and patients who received breast cancer treatment at Ellis-Fischel Cancer Center within the past three years will be identified. Those with self-reported CRCI will undergo further screening and eligible subjects will complete baseline assessment remotely. After baseline assessment, subjects will be randomized to one of two groups: (1) a 10-session CO-OP intervention; or (2) a 10-session attention control group. Block randomization will be used to ensure equal distribution between groups. The study statistician, Dr. Golzy will create and oversee the randomization sequence. Each CO-OP session will last 60minutes and subjects will complete one session per week over the course of 12 weeks. Subjects will under go the same assessment battery that was completed at baseline within one week post-intervention remotely.
    a. Cognitive Orientation to daily Occupational Performance (CO-OP). CO-OP is a metacognitive strategy training intervention that will be used in this study. First, five functional, everyday life goals are identified collaboratively by the participant and interventionist. In the second meeting, when CO-OP actually begins, we introduce the approach to the subject and teach the global cognitive strategy (i.e., GOAL-PLAN-DO-CHECK). In all subsequent sessions, this strategy is used as the main problem-solving framework to facilitate skill

acquisition. The subject identifies a GOAL, and then is guided by the therapist to discover a PLANt o potentially achieve the goal. The subject is then asked to Dot he plan (if feasible during the therapy session otherwise asked to complete at home prior to the next treatment session), and subsequently to CHECK to see if the plan worked, i.e. the goal was achieved. This process is repeated until satisfactory performance is met for each established goal.

b. Attention Control Group: Individuals in the attention control group will have dose-equivalent, weekly virtual contact through the Zoom platform for 10-weekswith an occupational therapist not involved in CO-OP treatment. The control group will control for interpersonal interaction, maturation effects, and testing effects. The focus of each session will include: (1) social interaction characterized by warmth/empathy and (2) provision of usual care CRCI educational resources (e.g. exercise, using memory aids, minimizing distractions) from MD Anderson Cancer Center. These recommendations will be provided without further instruction. Any questions that arise regarding CRCI the subject is experiencing will be answered. The therapist will debrief with the subject on any changes in CRCI symptoms. The content and duration of each call will be tracked.

2. The study duration is approximately 12weeks. This includes about 2.5 hours of pre-intervention assessments (Table 1), 10, 45-60 minute intervention sessions, and about 2 hours of post-intervention assessments.
3. All study procedures are for research purposes only.
4.

Table 1. Study Measures

Assessment	Construct	Score Evaluated	Administration Time	Specific Aim
Primary Outcome Measures				
Feasibility measures	Recruitment rate, retention rate	N/A	T2	1
Telehealth Usability Questionnaire (TUQ)	Telehealth Usability	Average Score	T2	1
Acceptability of Intervention Measure (AIM)[62]	Intervention acceptability	Total score	T2	1
Intervention Appropriateness Measure (IAM)[62]	Intervention appropriateness	Total score	T2	1
Feasibility of Intervention Measure (FIM)[62]	Intervention feasibility	Total score	T2	1

Canadian Occupational Performance Measure (COPM)[63]	Subjective activity performance	Average score across goals	T1, T2	2
NeuroQoL Cognitive Function Short Form[64]	Subjective cognition	T-score	T1, T2	2
Secondary Outcomes*				
Patient Health Questionnaire (PHQ-9)[65]	Depression symptoms	Total score	T1, T2	2
Functional Assessment of Cancer Therapy-Breast (FACT-B)[66]	Quality of Life	Total Score	T1, T2	2
Montreal Cognitive Assessment (MoCA)[67]	General cognitive function	Total score	T1, T2	2
Delis-Kaplan Executive Function System (DKEFS)-Color-Word Interference[68]	Inhibition, cognitive flexibility	Total score	T1, T2	2
Wechsler Adult Intelligence Scale (WAIS)-IV Letter-Number Sequencing, Coding, Symbol Search subtests[69]	Inhibition, attention, working memory, processing speed	Total score	T1, T2	2
Brief Visuospatial Memory Test –Revised[70]	Episodic memory	Total score	T1, T2	2
Paced Auditory Serial Addition Test[71]	Working Memory	Total score	T1, T2	2
Patient-Reported Outcomes Measurement Information System (PROMIS-57) Profile v2.0[72]	Self-reported changes in anxiety, depression, fatigue, pain, physical function, sleep, participation	T-scores for each domain	T1,T2	2
Additional Data Collected				
Medical record data	Medical history information	N/A	T1	N/A
Demographic data	Description of population	Age, race, gender, education level	T1	1,2

Therapy logs	Description of treatment provided	N/A	Continuously monitored	1, 2

5. *Also used to help identify possible covariates for future studies

VII. Potential Risks

1. There are minimal risks expected when taking part in this study. There are some that we know about and some may not know about yet. Some possible risks include (1) a breach of confidentiality where identifiable health information related to the participants is inadvertently made available to individuals beyond the research team; (2) psychological distress while discussing changes in your abilities following cancer treatment; or (3) physical injury.

2. To help lower these possible risks, we will keep participant information in a password protected file on a secure network that has restricted access. All data will be obtained by the study team will be for research purposes only and will be de-identified prior to data entry into our secure electronic database. Any hard copy data will be locked in filing cabinets in the private offices of the PI. All electronic data will be maintained on one web-based, secure, centralized database. The database will use the REDCap® platform and can only be accessed through two password protected portals. All data entered into the REDCap® database will be stored on University of Missouri secure servers and will have access restricted to only members of the research team. In the rare event participants experience psychological distress when answering questions during assessments, they will be reminded that they can decline to answer any questions that may make them uncomfortable and that participation is completely voluntary.

3. The table below provides information on how AEs will be reported in this study (see Table 1). The plan for reporting has been determined based on the severity of the AE and the study attribution of the AE per the definitions and categories previously discussed. The reporting timeframe meets or exceeds the reporting requirements of the University of Missouri IRB. All AEs will be reported to by the University of Missouri IRB. IRB will review these as they are reported and also annually when the protocol is renewed. All severe adverse events below will also be reported to the sponsoring IC Program Officer within the timeframe listed. The University of Missouri IRB maintains a log of all reported AEs, including all details related to the AE, actions taken, and outcomes, over the course of the study that will be used by the study team for tracking purposes.

Table 1: AE Reporting Plan

Study Attribution	Time for Reporting by type of AE		
	Mild	Moderate	Severe

Unrelated	Not required	Not required	5 days
Definitely Related	5 days	5 days	24 hours
Probably Related	5 days	5 days	24 hours
Possibly Related	5 days	5 days	24 hours

VIII. Anticipated Benefits

1. Participants may or may not directly benefit as a result of participation in the study. Information learned from the study may likely help other people in the future. Participants may potentially experience improvement in their ability to perform everyday life activities better and/or experience less cancer-related cognitive impairment.

IX. Compensation

1. Participants will be compensated for taking part in this study. For time and effort, participants will receive $75 via check payment within one month of pre-assessments and post-assessments for a total of $150.

X. Data Safety Monitoring Plan

Data Quality and Management

The research coordinator will oversee the review of all data collection forms on an ongoing basis for data completeness and accuracy, as well as protocol compliance. The table below is an overview of the schedule for data review (see Table 2). All data files completed during the specified time period will be reviewed. The study coordinator will assign a rater to review each file who was not the person who collected the data. The reviewer will complete an audit sheet to review the completeness and accuracy of each data file. Data verification will be completed on all outcome data by double data entry. All data will be entered into a separate electronic database. The research coordinator will cross-check the two data files and resolve any discrepancies. The results of the data verification will be reported on the audit form. All audit forms will be reviewed by the PI and further training of blind raters will occur if consistent errors are noted. Any protocol violations will be reported to the University of Missouri IRB.

Intervention fidelity and protocol adherence will be reviewed by Dr. Wolf (Co-I) with support from the CO-OP Academy, who is a certified trainer in the CO-OP approach. The CO-OP Academy has developed a CO-OP Fidelity Checklist that is used to monitor fidelity of the CO-OP intervention. This checklist will be completed by reviewing video recordings of intervention sessions and therapists must maintain an overall score of 80% to be compliant with the intervention. Any items missed on the checklist will be reviewed with the therapist during the next weekly meeting following the audit. Failure to maintain an 80% on any fidelity check will require individual instruction. For every participant, a minimum of two sessions are recorded: (1) one from sessions 2-5; and (2) one from sessions 6-9. Additional sessions may be recorded and reviewed at the Co-I's discretion, if therapists are consistently scoring at or below the 80% threshold.

Table 2: Schedule for Data Review

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Quarterly	Blind rater (confirmation by researcher coordinator and Dr.Boone, PI)
Status of all enrolled subjects, as of date of reporting	Quarterly	Blind rater (confirmation by researcher coordinator and Dr. Boone, PI)
Outcome data accuracy (double-data entry)	Quarterly	Blind rater (confirmation by researcher coordinator and Dr. Boone, PI)
Adherence data regarding study visits and intervention	Quarterly	PI
Treatment fidelity	Quarterly	Dr. Wolf, Co-I (with CO-OP Academy)
AEs and rates	Quarterly	PI

Subject Accrual and Compliance

Per Table 2 above, review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur quarterly during the 1.25 year recruitment phase to ensure that: (1) a sufficient number of participants are being enrolled; (2) participants are meeting eligibility criteria; and (3) the targeted ethnic diversity goals outlined in the grant proposal are being met (see *Inclusion of Women, Minorities, and Children*).

Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial

Safety Review Plan

Study progress and safety will be reviewed quarterly per above. Annual progress reports, including patient recruitment, retention/attrition, and AEs, will be provided to the University of Missouri IRB. The annual report will include a list and summary of AEs. In addition, the annual report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The annual

report will be provided to the sponsoring IC. The IRB and other applicable recipients will review progress of this study on an annual basis.

XI. Multiple Sites

1. N/A

XII. References

1. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review. *Cancer Treatment Reviews.* 2012;38(7):926-934.
2. O'Farrell E, MacKenzie J, Collins B. Clearing the air: a review of our current understanding of "chemo fog". *Current oncology reports.* 2013;15(3):260-269.
3. Reid-Arndt SA, Hsieh C, Perry MC. Neuropsychological functioning and quality of life during the first year after completing chemotherapy for breast cancer. *Psychooncology.* 2010;19(5):535-544.
4. Reid-Arndt SA, Yee A, Perry MC, Hsieh C. Cognitive and psychological factors associated with early posttreatment functional outcomes in breast cancer survivors. *Journal of psychosocial oncology.* 2009;27(4):415-434.
5. Cicerone KD, Dahlberg C, Kalmar K, et al. Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Archives of Physical Medicine and Rehabilitation.* 2000;81(12):1596-1615.
6. Cicerone KD, Langenbahn DM, Braden C, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Archives of Physical Medicine and Rehabilitation.* 2011;92(4):519-530.
7. Haskins E. *Cognitive Rehabilitation Manual: Translating Evidence-Based Recommendations into Practice.* Vol 1. Reston, VA: American Congress of Rehabilitation Medicine; 2012.
8. Wolf TJ, Doherty M, Kallogjeri D, et al. The feasibility of using metacognitive strategy training to improve cognitive performance and neural connectivity in women with chemotherapy-induced cognitive impairment. *Oncology.* 2016;91(3):143-152.