Mitigating Cancer-Related Cognitive Impairment in Older Adults with Breast Cancer Receiving Chemotherapy: Memory and Attention Adaptation Training-Geriatrics (MAAT-G) Phase I

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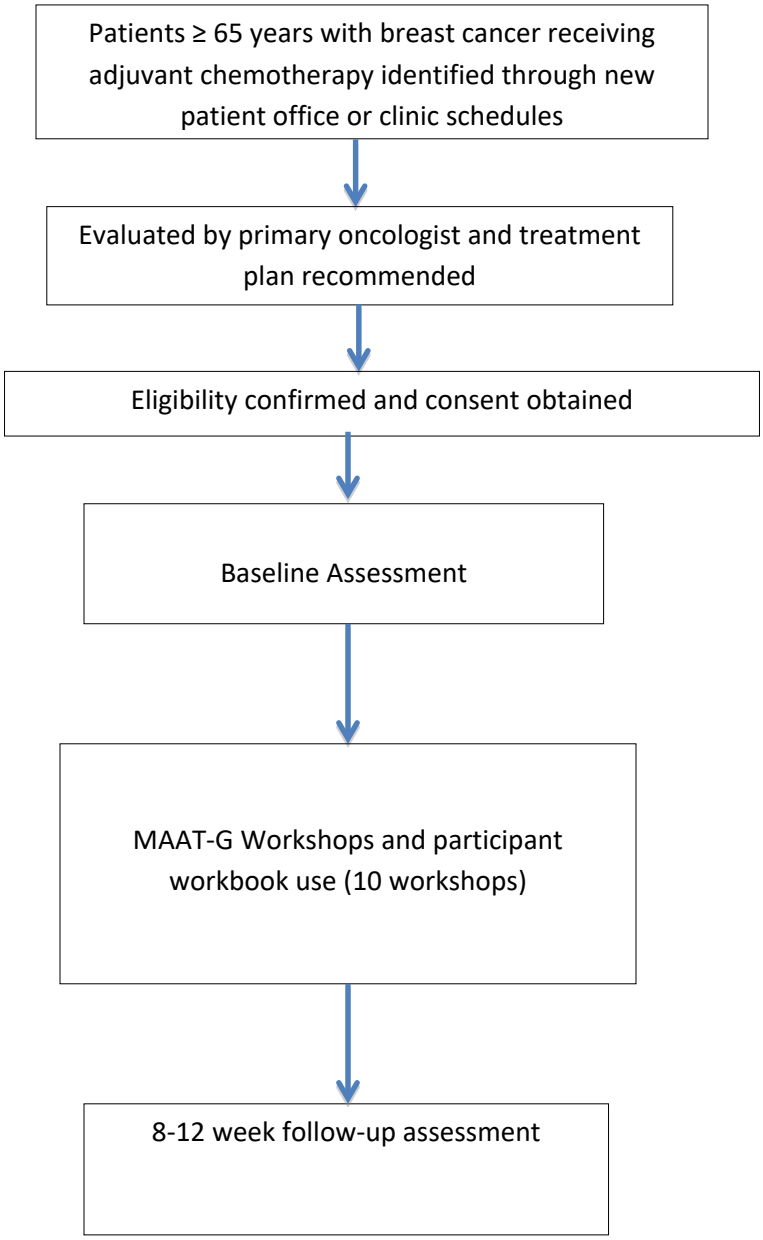
1.0 STUDY SCHEMA



2.0 SPECIFIC AIMS

Cancer-related cognitive dysfunction (CRCD) is a significant problem. Our group and others have demonstrated that CRCD affects up to 75% of patients during treatment and can create difficulties in attention, processing speed, executive function and memory.[1-3] Older adults are at greater risk of developing CRCD;[4-8] half of women aged ≥65 receiving adjuvant chemotherapy for breast cancer report worsening of cognition, and 25% have measurable declines on neuropsychological testing six months post-chemotherapy.[9,10] Patients with localized breast cancer have excellent overall survival but are at risk for CRCD as a long-term side effect of therapy.[11-13] For older adults, CRCD can compromise functional independence (e.g. Instrumental Activities of Daily Living [IADL]).[14] The etiology of CRCD likely involves multiple factors including host factors (e.g. age, cognitive reserve), biologic factors (e.g. cortisol-mediated stress response), clinical factors (e.g. comorbidities) and psychological factors (e.g. coping mechanisms).[2,15-20] While alleviating or preventing CRCD is important to older adult patients and their caregivers, interventions tailored to them do not exist.[21] Developing CRCD interventions for older adults is a high-priority area of research for the NIA.[22-25]

The Memory and Attention Adaptation Training (MAAT) intervention shows promise for targeting modifiable factors of CRCD.[11,26-28] MAAT provides instruction and practice with adaptive behavioral coping skills, stress management techniques, and compensation strategies for episodes of cognitive failure (e.g. lapses in memory, attention). MAAT is a series of eight manualized workshops delivered by a psychologist via video-conferencing combined with a participant workbook. In younger cancer survivors (i.e. those who have completed chemotherapy), MAAT improves self-perceived cognition (Functional Assessment of Cancer Therapy–Cognition [FACT-Cog], d=0.52), verbal memory (California Verbal Learning Test 2 (CVLT), d=-0.63) and processing speed (Symbol Digit Subtest of Telephone Based Neuropsychological Status [TBANS], d=0.5).[11,26] These cognitive functions are particularly important for older adults; however, MAAT has only been tested in a clinical trial involving younger survivors. MAAT requires adaptation to meet the unique needs of older adults in order to optimize usability and efficacy for this population (e.g. workshop content, workbook formatting). In addition, MAAT could be delivered alongside adjuvant chemotherapy to mitigate the development of CRCD (when risk is highest) and CRCD-related effects on functional independence for older adults, but more data are needed.

Study Objective:

Primary Objective: We will test the feasibility of delivering the adapted MAAT (MAAT-Geriatrics [G]) in older adults with breast cancer receiving adjuvant chemotherapy by determining usability of the intervention using the System Usability Scale (SUS).

Secondary Objective: To obtain descriptive feedback on the usability of the intervention and guide further adaptation, qualitative interviews with patients and their caregivers (if available) will be conducted at completion of the intervention.

3.0 BACKGROUND AND RATIONALE

3.1. Cancer-related cognitive dysfunction (CRCD) is a prevalent clinical problem; older adults are at greater risk of experiencing CRCD with cancer treatment, especially chemotherapy.[1-8,15,29,30] Symptoms of CRCD include problems with memory, attention and executive function.[2] CRCD is common; in the largest CRCD study to date, patients with breast cancer receiving adjuvant chemotherapy reported significantly greater cognitive difficulties from pre-chemotherapy to 6 months post-chemotherapy, compared to age-matched controls (mean change FACT-Cog score -10.4 in patients versus mean change +1.5 in controls).[1,2,15] Older patients, particularly those with lower cognitive reserve, may be most vulnerable to the effects of chemotherapy on cognition.[4-6,29,30] Ahles and colleagues observed that the subgroup of older patients with low baseline cognitive reserve prior to adjuvant chemotherapy for breast cancer had the largest decline in processing speed post-treatment.[4] Twenty-five percent of older women with breast cancer receiving chemotherapy develop cognitive decline from pre- to six months post-chemotherapy (defined as decline in 1 standard deviation in $\geq$ two neuropsychological domains)[10], and half report worsening of their cognition.[9] The effects of CRCD can be long-term; up to 35% report CRCD months to years after completing therapy; cross-sectional studies of older breast cancer survivors demonstrate lower performance in multiple areas of neurocognitive function compared to age-matched controls without cancer, even several years after treatment.[12,13]

3.2. Advances in breast cancer therapies have greatly improved survival rates; older patients are living long enough to experience long-term complications of treatment such as CRCD. The five-year overall survival rate for patients with early stage breast cancer (I-III) is 98.9% for localized disease (breast only) and 85.2% for regional disease (lymph node involvement).[11] Given these favorable cancer-related outcomes, CRCD and its functional consequences are particularly relevant for older adults with breast cancer. CRCD may create difficulties with Instrumental Activities of Daily Living (IADL), such as managing medications, which may compromise independence and quality of life for older adults.[7,14,31-33] Nearly one-third of older women receiving adjuvant chemotherapy for breast cancer experience functional decline 1 year post-treatment.[34] Despite this vulnerability, there are no available interventions to mitigate CRCD for older adults, because older adults are underrepresented in oncology clinical trials, and interventions to improve issues that are important to older adults, such as cognition, are not prioritized.[35-37] A geriatric oncology U13 conference series supported by the NIA, NCI, and CARG highlighted intervention development, particularly cognitive interventions, as a high priority area for research.[22,24,25,38,39]

3.3. Multiple factors are likely involved in the etiology of CRCD including host factors (e.g. age, cognitive reserve)**,** biologic factors (e.g. cortisol-mediated stress response), clinical factors (e.g. comorbidities) and psychological factors (e.g. coping mechanisms).[2,15-20] CRCD can be conceptualized using a diathesis stress model, whereas under routine and low stress conditions, cognitive failures of daily life (e.g. mental lapses in memory, attention) are likely to occur with less frequency and when they do, they are readily managed.[28] However, under periods of sustained physical and psychological stress (allostatic overload) such as chemotherapy, there may be dysregulation of the stress response leading to more frequent cognitive failures.[19] The threshold for allostatic overload is variable and depends on an individual's self-regulatory capacity (i.e. an individuals' limited fund of "mental energy" to attend to self-regulatory behaviors such as decision-making, attentional demands, and emotional regulation).[40,41] Coping involves monitoring self-regulatory capacity and recognizing situations of allostatic overload that require adjustment/adaptation of behaviors.[20] Maladaptive coping mechanisms can lead to further negative effects on cognition.[42] Additionally, individuals possess varying abilities to compensate for cognitive stressors; however, compensatory strategies can be taught.

3.4. Memory and Attention Adaptation Training (MAAT) is a cognitive-behavioral therapy (CBT)-based intervention for CRCD. MAAT was designed as a practical and short-term CBT intervention to help cancer survivors learn adaptive, compensatory skills for chemotherapy-related memory dysfunction. In the literature, cognitive rehabilitation involves 2 broad approaches. This distinction is important and remains a source of debate. Traditional cognitive rehabilitation, or a "retraining" approach, emphasizes practice and drill of cognitive exercises to promote neuro-circuitry repair of damaged brain regions. However, some investigators contend performance at everyday tasks requiring memory (e.g., "memory related disability") does not improve with the retraining approach or generalize or "transfer" to daily living. By contrast, a "compensatory strategy" approach emphasizes direct teaching of adaptive skills on everyday tasks, which require memory, to minimize the impact of memory dysfunction on daily quality of life and function. We believe the compensatory strategy approach is advantageous to the retraining approach as it may be completed in a shorter format better suited to adult survivors. It overlaps with theoretical principals of CBT; learning new behaviors and cognitions to promote therapeutic, adaptive change. Compensatory strategies used in MAAT include self-awareness training (self-monitoring record keeping to identify "at risk" situations where cognitive failures may occur), Self-Instructional Training (SIT), or a method of "self-talk" to enhance on-task attention, mnemonic strategies to enhance retention and retrieval for daily working memory, and organizational and social skills training such as keeping a simplified schedule or active listening skills. Self-regulation skills of applied relaxation training and activity scheduling/pacing are also included. The overarching aim of MAAT is to enhance self-management and coping with cognitive failures in daily life to minimize impact on survivor quality of life. As a CBT-based intervention, MAAT focuses on an individual's psychological response to injury as compared to the biological events triggering CRCD. MAAT is a series of manualized workshops delivered by a psychologist via video-conferencing, supplemented by a participant workbook, which provide instruction and practice with adaptive behavioral coping skills, stress management techniques, and compensation strategies.

3.5. The **scientific premise** of this new research is that CRCD is a significant problem, particularly for older adults, and interventions to improve cognitive outcomes are needed.

3.6 Preliminary Studies:

3.6a. Older patients and caregivers are concerned about the cognitive effects of chemotherapy. We conducted pilot work exploring goals with patients and caregivers in the SOCARE clinic. Patients and caregivers rated their goal to preserve cognition as high as cancer-related outcomes (e.g. improved survival) in the decision-making process for cancer treatment.[21]

3.6b. Nearly half of patients with breast cancer receiving adjuvant chemotherapy report a clinically significant decline in self-reported cognition.[1] Additionally, in this population frailty characteristics increased from pre- to post-chemotherapy; and importantly patients with worse perceived cognition at baseline had a greater number of frailty characteristics after chemotherapy.[47]

3.6c. It is feasible to study behavioral interventions in clinical trials for older adults with cancer receiving chemotherapy.[48] A pilot RCT testing the feasibility of implementing GA-guided management interventions for older adults with cancer receiving chemotherapy was conducted by the PI at the University of Rochester Wilmot Cancer Institute. 71 older adults were enrolled (75% of approached patients consented); 89% completed the 3-month follow-up assessment. A subset of older adults receiving chemotherapy experienced cognitive decline; in analysis of the Clock Draw Test, 15% demonstrated significant decline at 6-week follow-up.

3.6d. MAAT was pilot-tested in three separate studies of younger breast cancer survivors (n=29-47; mean age ranging 50-56 years).[11,26,27] Overall, MAAT improved perceived cognition (Functional Assessment of Chemotherapy-Cognition [FACT-Cog]) compared to active controls (p=0.02, d=0.52). For objective neurocognitive outcomes, MAAT participants demonstrated improved verbal memory (California Verbal Learning Test [CVLT]-2, p<0.05, d=-0.63) and processing speed compared to controls (Symbol Digit subtest of Telephone-Based Assessment of Neuropsychological Status [TBANS], p=0.03, d=0.5).[26] Specifically, the original MAAT program was brief and consisted of 4 (30-50 minute) office visits and 3 phone contacts. This was tested in pilot research using a single-arm study. Twenty-nine breast cancer survivors (average 8.2 years post-chemotherapy; SD = 4.4 years) completed MAAT. Principal outcome measures included self-reported cognitive function in daily life as assessed by The Multiple Ability Self-Report Questionnaire (MASQ) Quality of Life- Cancer Survivors scale, satisfaction ratings and a brief neuropsychological test battery. Testing occurred at 4 time points: baseline, post-treatment, 2-month and 6-month follow-up. Results indicated a significant reduction in self-reported daily cognitive complaints (MASQ), improved quality of life and high satisfaction ratings. Neuropsychological test score improvements were observed in tests of verbal memory and in processing speed. Finally, survivors reported high satisfaction with MAAT. The one-group design limited conclusions about efficacy and the effect of practice on repeat administration of neuropsychological tests, but pilot results warranted further MAAT study.

In a second study utilizing a wait-list control design, 40 women were enrolled and randomized to treatment (n = 19) or waitlist control (n = 21) conditions and assessed at baseline, post-treatment and 3 month follow-up time points. ANCOVA demonstrated two statistically significant outcomes controlling for effects of education and IQ: 1) the spiritual wellbeing subscale of the Quality of Life-Cancer Survivor Scale (QOL-CS); and 2) CVLT-2 Total Score. Effect size in verbal memory performance (CVLT-2 Total Score) among MAAT participants was large at post treatment even after subtracting the effect size observed in controls (.50).

In a third study, MAAT was delivered via televideo conferencing and patients were randomized to receive the MAAT intervention versus supportive therapy (control). One method of improving access to rural cancer survivorship services is through communications technologies. “Telehealth” refers to the use of a broad array of communications devices to improve health care access.

4.0 SUBJECT ELIGIBILITY

The eligibility criteria are aimed at identifying older patients undergoing cancer treatment. As above, if patients are able and willing to identify a caregiver, caregivers will also be consented to participate in study processes.

4.1. Patient Inclusion Criteria:

- Have a diagnosis of invasive breast cancer
- Planned to receive systemic therapy for breast cancer or actively receiving systemic therapy for breast cancer with two additional cycles remaining.
- Be age 65 or older
- Able to provide informed consent
- Able to read and understand English (or possess a designated health care proxy that can do the same that was designated prior to the patient losing decision-making capabilities)

4.2. Patient Exclusion Criteria:

- Have surgery planned within 3 months of consent
- Patients who do not have decision-making capacity (decisionally or cognitively impaired) **AND** do **NOT** have a previously designated health care proxy (established prior to their cognitive impairment) available to sign consent
- Patients with breast cancer receiving endocrine therapy as their only systemic therapy will not be eligible.

We anticipate enrolling up to 10 patients to phase I.

4.3 Entry criteria for caregivers:

A caregiver can be anyone, age 21 or over, who is able to understand spoken English, understand the study process and provide informed consent. One caregiver for each patient will be eligible and must be chosen by the patient. For the purposes of this study, a caregiver is defined as a valued and trusted person in a patient's life who is supportive in health care matters by providing valuable social support and/or direct assistive care.

4.3.1. Inclusion criteria for caregivers:

- Selected by the patient when asked if there is a "family member, partner, friend or caregiver [age 21 or older] with whom you discuss or who can be helpful in health-related matters;" patients who cannot identify such a person ("caregiver") will remain eligible for the study.

4.3.2 Exclusion criteria for caregivers

- Caregivers unable to understand the consent form due to cognitive, health or sensory impairment will be excluded

5.0 IDENTIFICATION, RECRUITMENT, AND CONSENT PROCEDURES

Subjects will be enrolled at the University of Rochester Comprehensive Breast Cancer Center at Pluta Cancer Center and the University of Rochester Wilmot Cancer Institute at Highland Hospital. Patients will be recruited from the breast medical oncology clinics at these two sites. The clinic schedules of breast oncologists and their advanced practice providers (APPs) will be screened for eligible patients.

To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subject Research will be followed.

5.1. Patient and Caregiver Identification, Recruitment, and Consent Procedures:

Potential patients will be identified in multiple ways. First, at the two sites for accrual, study participants will be identified by their treating physician, the nurses that work with the physicians, and the study coordinator. The study coordinator works closely with the physicians and nurses to monitor patients and identify those patients that are anticipated to begin cancer treatment. With permission from oncology providers, we will screen for eligible patients from clinic schedules. The study

coordinator contacts the physician (or their designee) and lets them know that a patient may be eligible for the study. The physician (or their designee) then confirms if the patient is a good study candidate or not and affirms that the patient has decision making capacity. If there is a question about eligibility, the principal investigator will be contacted and will meet with the patient and/or health care proxies, review the medical records, and perform an assessment of eligibility if necessary. After meeting with the physician (or their designee), the study coordinator will meet with the patient, and explain the details of the study. Study staff will introduce the study to the patients and provide adequate time to read the consent.

Recruitment of caregivers: If patients are agreeable to participating in the study, patients will be asked if there is a "family member, partner, friend or caregiver [age 21 or older] with whom you discuss or who can be helpful in health-related matters;" to participate as a caregiver. If patients are unable to identify a caregiver, they will still be able to participate. If patients are able to identify a caregiver, the study coordinator will give the patient a contact form that summarizes the purpose of the study, what the study would entail for the caregiver, and study coordinator's contact information. If the caregiver is interested in participating, s/he will contact the study coordinator using the contact information provided on the contact form. The study coordinator is not allowed to initiate the first point of contact with the caregiver.

5.1.1. *Informed Consent:* Informed consent will be obtained from the patient by the study coordinator in person during a clinic visit. The study coordinator uses the informed consent document as a written aid and goes over every detail of the study with the patient and/or health care proxy in person and recruits them to the study. The study coordinator, the oncologist and the nurses are available to answer any questions the patient may have about any aspect of the study prior to consenting and throughout the entire study period. Patients may choose to sign the informed consent immediately on the day the study information is presented to them or they may choose to take the informational consent form home and discuss it with others. If they want to participate in the study, they can sign it the next time they meet with the study coordinator or investigators. If the patient is participating in a telehealth visit and expresses interest, the coordinator will ask patient for his/her permission to be mailed an informational consent for their review.

5.1.2. *Verbal Informed Consent:* If the patient or caregiver cannot meet in person with the study coordinator to sign the informed consent, the study coordinator will verbally consent the subject. The study coordinator will use the verbal consent script, then sign and date it to confirm that s/he followed the script and the subject agreed to participate in the study. Following the completion of verbal consent with the subject, the coordinator will mail or email the subject a study information sheet that summarizes what the study entails and the subject's involvement in it.

5.1.3. *Baseline Measures and Study Procedures:* The baseline measures will then be performed and study procedures will occur. The patient must be determined to have decision-making capacity to provide informed consent by their treating oncologist.

5.1.4. *Human Subject Protection:* Ethical standards for human subjects will be strictly followed in accordance with the University of Rochester Research Subject Review Board Investigator Guidance policy and the University of Rochester Policy on Enrollment of Adult Decisionally Incapacitated Research Subjects and Permission of Authorized Representatives.

5.1.5. *Participation:* Current, state, federal, and institutional regulations concerning informed consent will be followed. Participation in this study is voluntary. Participants are free not to take part or to

withdraw at any time, for whatever reason, without risking loss of present or future care they would otherwise expect to receive. In the event that a patient does withdraw from the study, the information they have already provided will be kept in a confidential manner. Participants may discontinue participation in the study at any time if they decide they do not wish to take part any longer. Participants may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate.

5.1.6. *Duration:* Patients who consent to the study will be in this study for five months. Patients will be consented to actively participate, receive phone calls or meet with the research study team for up to 5 months after their initial visit. The research team may contact patients in the future to gain further information first hand regarding patients' overall health and treatment. Dr. Magnuson may decide to take patients off the study without their consent if the study is stopped. Additionally, patient data will be kept indefinitely at URMC, even after the study is closed or a patient passes away. It will be maintained in a locked database with password access only (See Section 8).

6.0 REGISTRATION AND RANDOMIZATION

6.1. Registration:

To register a participant and caregiver who meets the eligibility criteria and who has signed the informed consent document, study staff will enter the information outlined in section 6.2 in the OnCore database.

6.2. Information Requested at Registration:

6.2.1 First name
6.2.2 Last name
6.2.3 eMRN
6.2.4 Birth Date
6.2.5 Gender
6.2.6 Race
6.2.7. Ethnicity

6.3. Initial Assessment:

After consent procedures are completed, the patient, with the help of the study coordinator, will complete a baseline assessment (See section 7). For phase I of this study, there will not be randomization of subjects.

7.0 TREATMENT PROTOCOL

7.1 Measures:

Patient measures will include *demographics, cognitive, psychological, and functional independence* measures. The battery was selected based upon our experience in prior studies.[1,26,50,51] Based upon experience in prior studies, we estimate the cognitive evaluation will take approximately 60 minutes to

complete[1,3] and the demographics, psychological and functional independence measures will take approximately 20 minutes.

Demographics: Patient and caregiver demographics will be collected, including age, gender, race, ethnicity, marital status, education and socio-economic status will be captured. Cancer and treatment variables, comorbidities, and medications list will be collected from the medical record by study staff.

Cognitive Evaluation will include: 1) FACT-Cog[52], a validated patient reported outcome measure created to assess cognitive challenges identified by patients with cancer; 2) Cambridge Neuropsychological Test Automated Battery (CANTAB) delayed match to sample test[53] (DMS), Rapid Visual Information Processing (RVP), and Paired Associates Learning (PAL), validated, computerized tests that assess short-term visual/spatial memory, sustained attention, and visual memory/new learning; 3) Controlled Oral Word Association (COWA)[54], a measure of verbal fluency evaluating expressive language and executive function; and 4) Hopkins Verbal Learning Test-Revised (HVLT-R)[55], a validated test of verbal learning and memory. All measures are "paper and pencil", except for the CANTAB (computer-based assessments that, due to COVID-19, will be administered virtually by collecting patients' emails and sending a web-based link). COWA and HVLT-R require the study coordinator to administer the tests; they can be administered virtually so study coordinator will schedule a telephone or televideo meeting with the patient at the corresponding time points, as needed.

Psychological Assessment: will include Geriatric Depression Screen (GDS)[57] and Generalized Anxiety and Depression (GAD-7).[58]

Functional Independence: IADLs will be measured.[59]

Usability will be assessed quantitatively with the System Usability Survey.[60,61]

Phase I semi-structured interview questions for patients and caregivers will focus on usability of MAAT-G (e.g. barriers and facilitators to intervention).

7.1 Study Procedures:

Baseline: Following informed consent, patients will undergo Time Point (TP) 1 assessment. Patients will be provided with a data-enabled tablet with HIPPA-compliant video-conferencing application and instructed on its use, participant workbook, and tablet instruction manual. At the time of enrollment, the study coordinator will assign each patient a unique meeting ID number within the tablet instruction manual. This meeting ID number allows each patient to log on to the video-conferencing application and speak to the psychology fellow for the workshops. Study coordinators will train and support patients on the use of the tablet and video conferencing application. No data is being stored on the tablet itself. If patients consent to have sessions recorded, this will be done through the HIPPA-compliant Zoom software application. If participants do not have access to wireless internet, the tablet will be equipped with a data package for participant use for the purposes of this study. At completion of the study, patients will return the tablet to the study coordinator. If the tablet is lost or stolen during the study, no PHI will be stored on the tablet and thus would not be accessible. If the tablet is broken during the course of the study, we will provide participants with another tablet for use during the study period. The

participant would contact the study coordinator with any concerns or problems with using the tablet, contact information will be provided during training on tablet use.

Intervention Period: The intervention period is 8-10 weeks; 10 weekly MAAT-G workshops will be delivered through video-conferencing on the tablet. MAAT-G workshops will be audio-recorded for fidelity review. (See section 7.2)

Follow-up: Within 2-4 weeks of intervention completion (approximately week 10-12), patients will undergo TP2 assessment.

Patient assessments will be performed by trained study coordinators. As a safety precaution due to COVID-19, patients may take surveys home for completion (e.g. demographics) and then mail back to study team in order to minimize the amount of in-person contact between coordinators and patients; the method of completing surveys at home has been successful in prior studies with good retention.[43,48] However, to encourage the completion of the surveys, the study coordinator will schedule a telephone or televideo meeting with the patient, as needed, to ensure patients' questions concerning the surveys are addressed. Study coordinators will score assessments and transcribe results into a database. Audio-recordings will be deleted following transcription.

Semi-structured interviews will be conducted by a trained study coordinator who is not responsible for any other component of the study. Interviews will be conducted with patients and if consented, will include caregivers. As a safety precaution due to COVID-19, the interviews with the patients and caregivers will be conducted over the phone. These audio-recorded interviews will be conducted after completion of the intervention.

Intervention Adaptation: We will iteratively adapt the intervention through the course of Phase I based upon feedback from patient and caregiver interviews (i.e. adaptation after enrollment of subset of 3-4 patients).[62-64] We will iteratively revise the MAAT-G intervention based upon two sets of evaluations (System Usability Survey [SUS] and qualitative interview feedback). These evaluations will be conducted to determine how the MAAT-G intervention needs to be adapted to key human factors, such as vision and comprehension. Participants will be interviewed after completion of the intervention to gain feedback on the usability of MAAT-G via televideo conferencing and the utility of workshop sessions and workbook material. The information gathered in these one-on-one interviews will allow us to iteratively refine the MAAT-G intervention, testing each iteration with 2-3 patients before refining. Data gathered via audio-recording will be destroyed after transcribed.

Location: MAAT-G participation will take place through video-conferencing. Participants will be encouraged to participate from their home or other private location. Due to COVID-19, the Department of Psychology is conducting clinical visits from their clinical office and home office locations until further notice. Wherever the location may be, psychologists who are conducting the MAAT-G intervention will ensure privacy in a private room with a closed door. Participants will be provided with a HIPPA compliant tablet to use for participation in the intervention activities and the intervention will be delivered using HIPPA compliant video-conferencing technology provided by the University of Rochester. The coordinator will be in touch with patients by phone throughout the length of the study, serving as a liaison between patient and psychology fellow. Coordinator will help organize the scheduling/rescheduling of workshop sessions and will be available for any patient questions.

7.2. MAAT-G Intervention

The MAAT-G intervention will be delivered by a trained psychology fellow at the University of Rochester Medical Center. The intervention will be delivered through televideoconferencing and participants will be provided a tablet equipped with a HIPPA compliant televideoconferencing application to use for the MAAT-G workshop sessions. We will use the University of Rochester Zoom application which is HIPPA

compliant. A tablet instruction manual will be given to patients to help guide them through how to use a tablet and how to navigate the Zoom application. A unique meeting ID number will be given to each patient to log in to the Zoom application. If participants do not have access to wireless internet, the tablet will be equipped with a data package for participant use for the purposes of this study. Participants will also be provided a workbook for skills practice in between workshop sessions. A summary of workshop content is provided in table 1 below.

Table 1: MAAT-G workshop content**WORKSHOP VISIT:**	Content/Strategies:
1	• Introduction to MAAT • Self-Awareness and monitoring of memory problems
2	• Progressive Muscle Relaxation • Quick Relaxation
3	• Self-Instructional Training • Verbal and silent rehearsal
4	1. Cognitive restructuring
5	2. Keeping a schedule • Memory routines
6	1. External cueing • Distraction reduction
7	1. Activity scheduling and pacing 2. Active listening
8	1. Fatigue management 2. Sleep improvement
9	• Visualization strategies
10	• Tying it all together

7.3. Potential risks:

A participant may become more aware of any attention or memory problem they are experiencing as a result of participation in this study, potentially increasing psychological stress. While this is unlikely to provoke significant problems, the PI (Dr. Magnuson) will be available for evaluation and referral to appropriate behavioral care if needed.

Risks to privacy using telehealth and telecommunications are a potential concern. We also recognize that while encryption of videoconferencing makes breeches of private information unlikely, not all risks to privacy can be completely eliminated. We will inform all participants using the telehealth equipment of this.

7.4. Potential benefits:

There may be no direct benefits to participation in this study. However, the study will provide useful information about chemotherapy-associated cognitive problems for older adults and strategies for helping patients cope with memory and attention problems.

8.0 DATA MANAGEMENT

8.1. Data Handling and Statistical Considerations:

8.1.1. The same protocols and procedures for data quality and control that are readily used for prior studies conducted with the Geriatric Oncology Research Group and currently being overseen by our office. Data will be entered into REDCap (see section 8.3.5 below).

8.1.2. After entering into REDCap, data are audited visually for errors. R, SPSS and SAS will be used for the statistical analyses. Unless otherwise stated, all statistical tests will be performed at the two-tailed 5% level of significance. Likewise, 95% confidence intervals will be constructed for the estimation of effects.

8.1.3. The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.[65,66] In case of violations of distribution assumptions such as normality, appropriate nonparametric methods will be attempted.[67,68] If outliers or influential data are detected, the accuracy of the data will be investigated. If no errors are found, analyses may be repeated after removing these cases to evaluate their impact on the results. However, the final analyses will include these data points.

8.2. Data Analysis and Sample Size:

Phase I Data Analytic Plan:

Quantitative Analysis: The SUS ranges 0-100; a score >68 is above average.[61] Our goal will be to achieve a score >68 after iterative adaptations. Because we are using the SUS to guide iterative adaptations to the intervention, the SUS score will be evaluated within the group of patients receiving each iterative version of the intervention (e.g. 2-4 patients) and not the overall group of patients enrolled. Although the goal of iterative adaptations is to improve the usability (e.g. increase the SUS score through adaptation), there is a possibility of decrease in SUS score with subsequent iterations. If this occurs, further iterative testing will continue to achieve the target SUS.

Qualitative Analysis of transcripts from participant/caregiver interviews will be analyzed for themes on barriers and facilitators. Potential themes include relevance of workshop content to older adults, potential barriers to using video-conferencing technology for the target population and mechanisms for minimizing this barrier, and/or the content and formatting of participant workbook to ensure relevance and usability for older adults.

Phase Ib Mixed Methods Integration: Qualitative and quantitative data will be integrated to develop a more complete understanding of the usability of MAAT-G and potential areas for further adaptation (**Table 2**). Qualitative data will be analyzed first and then integrated with quantitative usability data to guide further adaptation of MAAT-G to improve usability. Data will be organized using MAXQDA joint displays.[70] Integrated analysis will guide further iterative adaptation.

Objective	Data Collection Procedures	Analysis Procedures	Point of Integration	Example of Integration Guiding Adaptation at each iterative adaptation cycle (3-4 dyads)
Adapt MAAT, for older adults using feedback from 10 patient and caregiver dyads	• Usability scale (*Quant*) • Semi-structured interviews (*Qual*)	• Descriptive statistics • Theme analysis guided by Phenomenology	• *Merging* (qual and quant are brought together for analysis) • *Building* (integrated results informs MAAT-G adaptation)	We will compare themes between patients with Health-ITUES scores above and below 68 to identify barriers and facilitators to intervention (e.g. If patients report difficulty absorbing the amount of material in each workshop session, we may increase the number of sessions to decrease information intensity per session).

8.3. Records to be Kept:

8.3.1. *Data Collection Table:*

FORM	SCHEDULE OF DATA COLLECTION	
	Baseline	**Post-Intervention**
On Study Data (Patient and caregiver demographic information and clinical data)	X	
FACT-COG	X	X
CANTAB	X	X
COWA	X	X
HVLT-R	X	X
GDS	X	X
GAD-7	X	X
IADL Survey	X	X
SUS (usability measure)		X

Semi-structured interview with patient and caregiver (if enrolled)		X

8.3.2 All hardcopy research records will be stored onsite in the University of Rochester Medical Center, in locked research files at the James P. Wilmot Cancer Center. The Cancer Center is secured with electronic key cards. Offices within the Cancer Center are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the University of Rochester Medical Center's password secured and firewall protected networks. These are the same methods of security used for patient medical records. All study data will be kept for a period of 10 years after the study and all reports and publications are complete.

8.3.3 All recorded data, such as the audio-recorded interviews/transcripts and Zoom workshop sessions, will be stored on the UR Box drive to assess fidelity of intervention delivery. Within the Box drive, data will be stored in a password protected folder with access restricted to the PI and a subset of study team members. All personal identifiers will be deleted (e.g. de-identified) from the transcriptions of the audio-recordings. Once data is uploaded to the secure server, the data will be deleted from the audio recorders.

8.3.4. All data collected for the current study will be used in post hoc analyses as appropriate. Data will not be used for future studies without prior consent of the patient. The patient's individual research record will not be shared with their treating physician, unless they provide consent or the patient's treating physician is a study physician, in which case they will have access to study data as a study co-investigator. Overall study results will be presented to participants, faculty and staff at the University of Rochester Medical Center after completion of the study. Study results will be presented at professional meetings and published.

8.3.5. The study coordinator will assign a numerical study ID to each participant once they have signed the consent form. All study forms and questionnaires will use this number and the participant's first, middle, and last initials as identifiers, to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with study ID, name, and contact information will be maintained separately. This linkage information will only be accessible to the study coordinator, study investigators, and the individuals responsible for maintaining the database.

8.3.6. Additionally, the data can be collected and managed by the research teams at University of Rochester Medical Center using REDCap[167] electronic data capture tools hosted at URMC.

> **8.3.6a**. URMC provides the following information on the REDCap program: "Vanderbilt University, in collaboration with a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data, called REDCap (Research Electronic Data Capture). The REDCap system is a secure, web-based application that is flexible enough to be used for a variety of types of research. It provides an intuitive interface for users to enter data and real time validation rules (with automated data type and range checks) at the time of data entry. REDCap offers easy data manipulation with audit trails and functionality for reporting, monitoring and querying patient records, as well as an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Through the REDCap Consortium, Vanderbilt has disseminated REDCap for use around the world.

Currently, over 240 academic and non-profit consortium partners on six continents with over 26,000 research end-users use REDCap" [168].

8.3.56. According to the Clinical and Translational Science Institute (CTSI), REDCap is supported with the following means. "The *CTSI Informatics Core*, a unit of the SMD *Academic Information Technology (AIT) Group,* will serve as a central facilitator for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team, with planning assistance from the *AIT-CTSI Informatics Core*. The iterative development and testing process results in a well-planned data collection strategy for individual studies"[168.]

8.3.6c. The CTSI states that regarding security, "REDCap servers are housed in a local data center at the University of Rochester and all web-based information transmission is encrypted. REDCap was developed in a manner consistent with HIPAA security requirements and is recommended to University of Rochester researchers by the URMC Research Privacy Officer and Office for Human Subject Protection.[168]

9.0 DATA SAFETY AND MONITORING

This protocol should be considered low risk as the intervention is a cognitive behavioral therapy (CBT)-based intervention. CBT- based treatments are utilized in routine clinical care for use with community dwelling older adults. This study is designed to see if MAAT, a CBT-based intervention, is feasible to deliver to older adults receiving adjuvant/neoadjuvant chemotherapy for breast cancer and can improve cognitive outcomes for this population..

9.1. Adverse Event Reporting Requirements:

9.1.1. Adverse events will be reported using the URCC Adverse Event form and/or as required by the Cancer Center Clinical Trials Office.

9.1.2. Adverse events will be reported in accordance with the following guidelines:

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and	Unexpected		Expect	Unexpected		Expected		Unexpe	Expect	Unexpect	Expect
		with hospit	witho ut		with hospi	witho ut	with hospit	witho ut				
Unrelated Unlikel	Not Required	Not Required	Not Required	Not Required	Not Requ ired	Not Required	Not Required	Not Required	10 Calenda r Days	Not Required	10 Calendar Days	10 Calend ar Days
Possible Probabl	Not Required	10 Calen dar	Not Required	Not Required	10 Calen dar	10 Calen dar	Not Required	Not Required	24-Hour; 5	10 Calend ar Days	24-Hour; 5 Calendar	10 Calend ar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

9.1.3. Adverse event reports will be submitted in one of the following ways:

(1) By email: (pdf)

(2) By mail:
(3) By fax:

9.1.4. An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risk information. This is a low risk study as interventions have been shown to improve outcomes of community-dwelling older adults.

9.1.5. A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. We anticipate that any serious events will be related to standard of care cancer treatment and not due to the MAAT-G intervention, which is designed to improve outcomes and focus on cognitive side effects of cancer treatment.

9.1.6. Adverse events will be reported in accordance with institutional policies (University of Rochester, Research Subject Review Board, local IRB, URCC CCOP, CTO, and DSMB) as per their requirements.

9.2. Data Safety Monitoring:

9.2.1. All adverse events requiring reporting will be submitted to the current Project Coordinator as described in Section 9.1. Serious adverse event reports will be forwarded to the study chair and the Data Safety and Monitoring Committee (DSMC). Adverse events are entered into a protocol-specific spreadsheet.

9.2.2. Adverse event rates are monitored utilizing the spreadsheet. If a serious adverse event is reported frequently, the study chair will conduct a detailed review. The DSMC Committee Chair will be notified and will determine if further action is required.

9.2.3. The Data Safety Monitoring Committee (DSMC) will review study progress and cumulative reports of adverse events at annual meetings and as needed. An overall assessment of accrual and adverse events will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure.

9.2.4. The URCC will notify the other sites immediately of any serious safety concerns identified by the DSMC.

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