PROTOCOL AMENDMENT #__10__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) We have modified Section 5.3 to include more specific dose reduction and stopping rules based on toxicity grade, attribution, and effect on chemotherapy treatment. We have also clarified that participants will be assessed for toxicities on a weekly basis during the titration period.
(3) We have updated Section 8.1.2 to clarify that the worsening of severity and frequency of adverse events will be evaluated when assessing causality.

Per correspondence with the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __4/23/21__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__9__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(4) The version date was updated throughout the protocol.
(5) We have added Yara Abdou, MD as a co-investigator to the study.

Per correspondence with the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __12/14/20__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__8__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) We have added language in Sections 1.1, 7.1, 7.2, 7.4, 7.5, and 9.1 to indicate that we have expanded study recruitment to include UNC REX Oncology clinics.

Per correspondence with the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __10/7/20__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__7__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(3) The version date was updated throughout the protocol.
(4) We have added details to Section 1.1, Section 5.6, Section 7.1, Section 7.5, Section 9.1, and Section 9.3 to clarify plans for extended longitudinal follow-up procedures for a subset of participants who voluntarily opt-in (i.e. cognitive and other secondary outcome measures will be repeated at 6 months post-chemotherapy). The plan to offer longitudinal follow-up for a subset of interested participants was indicated and approved in previous submissions, but these changes provide the details of this plan.
(5) We have added exploratory objectives in Section 2.3 and exploratory endpoints in Section 3.3 to coincide with the addition of the longitudinal follow-up procedures at 6 months post-chemotherapy for a subset of participants.
(6) We have updated survey language in Appendix F to include all gender identities.

Per correspondence with the PRC Coordinator, this amendment is exempt from PRC review.

PROTOCOL AMENDMENT #__6__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) We made a minor change to Section 5.2 to remain consistent with a previous amendment that widened the post-chemotherapy assessment window.
(3) We made a minor change to Section 1.1 to remain consistent about the timing of the baseline cognitive assessment throughout the protocol.
(4) We have changed Sections 5.8.18, 7.1, and 7.4 to specify that all participants will be asked to complete the Hormonal Status Questionnaire at the post-chemotherapy assessment.
(5) We have changed Section 7.2 to indicate that we have expanded study recruitment to include UNC Hillsborough Oncology Clinic.
(6) We modified Section 7.4 to remain consistent with a previous amendment that specified that we will utilize a wider range of options for dissemination of study assessments and surveys (i.e. email, phone, mail, online, and video conferencing methods).
(7) We have made changes throughout the protocol to reflect the addition of two new secondary outcome measures (RVP and OTS) that can be completed virtually to replace one measure (TMT) that must be completed in-person. This change will not affect our statistical plan and is being implemented so that every aspect of our study can be completed remotely.
(8) In Section 5.3 and 7.3, we have specified that toxicity assessments will occur at an interval no greater than every three weeks, instead of every 2 to 3 weeks depending on the timing of the chemotherapy regimen.
(9) In Section 5.3, we have stated that participants may decrease or discontinue memantine at any time, even in the absence of a memantine-associated toxicity.

Per correspondence with the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __5/21/20__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__5__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) We have made changes to Sections 1.1, 7.1, and 7.4 to widen the post-chemotherapy assessment window. While we will make every attempt to schedule assessments on their ideal dates, this will allow us more flexibility in scheduling in light of COVID-19 policy.
(3) We have made changes to Sections 1.1, 5.2, and 7.3 to reflect the potential expansion of study duration as a result of widening the post-chemotherapy follow-up window.
(4) We have made changes to widen the study drug start window in Sections 5.2, 5.5, and 7.3. We will make every attempt to start participants on our drug during the original schedule outlined in our PRC protocol, but this will allow for more flexibility in ensuring that participants have received our study drug prior to starting chemotherapy.
(5) We have made modifications Section 7.2 to utilize a wider range of options for dissemination of study assessments and surveys. We plan to implement email, phone, mail, online, and video conferencing methods of completing study assessments and questionnaires whenever possible in cases that in-person communication is restricted or prohibited.

Per correspondence with the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __3/13/20__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__4__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) We have added Timothy Brotherton, MD as a co-investigator to the study.
(3) We have added Section 5.8.18 and Appendix O and modified Sections 5.1, 5.7, 7.1, and 7.4 to reflect the addition of the Modified Brief Medication Questionnaire (BMQ)-Specific questionnaire. The Modified BMQ-Specific will be used to assess participants' beliefs about the necessity and concerns of taking memantine. The survey will be administered to participants at the post-chemotherapy assessment and offered upon study withdrawal, if applicable.

Per the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __1/13/20__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__3__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(6) The version date was updated throughout the protocol.
(7) We have added Kirsten Nyrop, PhD as a co-investigator to the study.

Per the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __11/21/19__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__2__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
_X_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) In Section 7.2 we have broadened the language regarding the location of study assessments to include participants' homes, which will allow for more flexibility in conducting cognitive assessments prior to the start and at the end of chemotherapy.

Eligibility changes

(1) In Section 4.2 we have updated our eligibility criteria to no longer specify severe renal impairment, defined as Cr > 3 mg/dL or CrCl < 30 mL/min, or total bilirubin > 2.5 mg/dL as exclusion criteria. These lab-based criteria have been removed because (1) neither are contraindications to receiving memantine (not listed on the package insert) and are (2) not available in most patients until the start chemotherapy (after our recruitment window).

Per the PRC Coordinator, this amendment is exempt from PRC review.

THE ATTACHED VERSION DATED __10/1/19__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__1__

LCCC 1921: Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

Editorial, administrative changes

(1) The version date was updated throughout the protocol.
(2) In Section 1.1 we have changed the language around the timing of cognitive assessments to allow for more flexibility in scheduling with participants.
(3) In Section 7.2 we have broadened the allowable methods of contact for study assessments to include over the phone.

Per the PRC Coordinator, this amendment is exempt from PRC review.

April 2017

THE ATTACHED VERSION DATED __8/26/19__ INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

April 2017

LCCC 1921:
Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

Short Title: Memantine for Prevention of Cognitive Decline in Patients with Breast Cancer

Principal Investigator
Zev Nakamura, MD
[redacted]
Email: zev_nakamura@med.unc.edu

Medical Monitor
Zev Nakamura, MD
[redacted]
Email: zev_nakamura@med.unc.edu

Co-Investigator(s)
[redacted]

April 2017

[redacted]

April 2017

Biostatistician

[redacted]

Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: North Carolina Clinical and Translational Sciences Institute (NC TraCS Institute), Grant #5K12HD001441-19

Version 1 Date: 6/22/2019
Version 2 Date: 8/26/2019
Version 3 Date: 10/1/2019
Version 4 Date: 11/21/2019
Version 5 Date: 1/13/2020
Version 6 Date: 5/21/2020
Version 7 Date: 9/4/2020
Version 8 Date: 10/7/2020
Version 9 Date: 12/14/2020
Version 10 Date: 4/23/2021

LCCC 1921:
Memantine for Prevention of Cognitive Decline during Adjuvant or Neoadjuvant Chemotherapy in Patients with Breast Cancer

Principal Investigator
Zev Nakamura, MD
[redacted]
Email: zev_nakamura@med.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Zev Nakamura M.D.

PI Signature: [redacted]

Date: 4/23/2021

Version date: 4/23/2021

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a one-arm phase II interventional study in patients with breast cancer to investigate whether memantine can prevent cognitive decline during chemotherapy. We will recruit 56 participants with breast cancer referred to the UNC Breast Center, Hillsborough Oncology, or UNC REX Oncology clinics for initiation of adjuvant or neoadjuvant chemotherapy, perform a cognitive assessment at initiation (range: any time after establishing care to one week after first dose) and four weeks after completion of chemotherapy (range: two to twelve weeks after last dose), and treat with memantine 10 mg twice daily between the pre- and post-chemotherapy study assessments (estimated duration: 12-30 weeks). We will assess cognitive function objectively using a computerized cognitive assessment and a standard neuropsychological battery. To assess subjective cognitive function, we will use the Patient Reported Outcome Measurement Information System (PROMIS) Cognitive Function measure. Depression, anxiety, fatigue, menopausal status, and sleep are comorbidities known to affect cognitive function, and therefore will be assessed as covariates through self-report measures and, in the case of menopausal status, laboratory values. Depression, anxiety, health-related quality of life (HRQOL) and functional status will be evaluated as secondary outcomes. Cognitive and other secondary outcome measures will be repeated in a subset of participants who opt-in for longitudinal follow-up at 6 months (range: 4 to 8 months) post-chemotherapy. We will also assess the feasibility of our study by monitoring recruitment, retention, and adherence to memantine.

1.2 Disease Background

Cancer-related cognitive impairment (CRCI) refers to a constellation of problems with memory, attention, and executive function that is associated with cancer and its treatments. There are over 16 million cancer survivors in the United States[1] and an estimated 5.5 million suffer from CRCI.[2] Specifically, up to 75% of patients with cancer report cognitive deficits during active treatment and up to 35% of survivors will demonstrate cognitive impairment on neuropsychological assessment (NPA) that can last years after treatment.[2] CRCI can have profound consequences, including inability to return to work,[3,4] reduced quality of life,[5–7] and doubled risk of dementia[8]. Given the substantial personal and societal burden of CRCI, and the absence of ways to prevent it, approaches that screen for CRCI and deliver effective interventions as soon after cancer diagnosis as possible are needed.

Most interventions for CRCI, including cognitive training and rehabilitation,[9–11] physical activity,[12,13] and meditation[14–16], however, are administered years after cancer treatment and have yielded inconsistent results. Perhaps the most essential study design issue impacting the efficacy of interventions is the timing of their

delivery relative to when cognitive issues are first appreciated. Specifically, because symptoms can persist for several years after cancer treatment and cognitive deficits are associated with underlying functional and structural brain changes, the extent to which CRCI is reversible is not clear.[17–22] Another critical variable impacting reliable interpretation of intervention efficacy is lack of agreement about how to measure CRCI. Self-report instruments are criticized as potentially reflecting other comorbidities (e.g. depression, anxiety, fatigue),[23–27] while other investigators raise concerns about the sensitivity[25] and ecological validity[28,29] of NPA. Further, despite International Cognition and Cancer Task Force (ICCTF) guidelines,[30] neuropsychological batteries used in research remain highly heterogeneous.

Evidence for pharmacotherapies for either prevention or treatment of CRCI is even more limited than with other CRCI interventions. To date, the only pharmacologic agents studied for CRCI include psychostimulants, supplements, epo-stimulating agents, donepezil (an acetylcholinesterase inhibitor), and memantine. Clinical trials with psychostimulants have demonstrated poor recruitment and retention rates;[31–36] supplements, including vitamin E and ginkgo biloba, have not been efficacious;[37,38] epo-stimulating agents have shown mixed efficacy,[39–43] but are no longer appropriate for use in CRCI following a 2011 Food and Drug Administration (FDA) black box warning regarding increased serious cardiovascular and thrombotic events that may shorten overall survival in patients with cancer;[44] and while donepezil may be an encouraging option,[45,46] it has not been studied for CRCI prophylaxis.

Compared to other pharmacotherapies, memantine is particularly promising for attenuation of chemotherapy-related cognitive decline in breast cancer for several compelling reasons. First, its mechanism of action targets cytokine-mediated damage suspected to cause CRCI. TNF-α, an inflammatory cytokine that is elevated in cancer, has been shown to contribute to glutamate excitotoxicity implicated in many neurodegenerative disorders.[47] Of interest, in a murine model, synergistic co-activation of TNF-α and N-methyl-D-aspartate (NMDA) receptors resulted in neuronal cell death, which was prevented by memantine through antagonism of the NMDA receptor.[48] Second, memantine is well-tolerated and does not interact with chemotherapies or other medications routinely used in breast cancer treatment. Third, memantine has been studied for CRCI prophylaxis in other aspects of cancer care.[49] Brown et al. investigated memantine for prevention of cognitive impairment in patients receiving whole brain radiotherapy.[49] Compared to placebo, memantine delayed time to overall cognitive decline and reduced the magnitude of decline in memory, executive function, and processing speed. There are several clinical trials underway building on this promising evidence for cognitive impairment due to cranial radiation, but memantine has not yet been tested to mitigate chemotherapy-related cognitive decline.

1.3 Current Standard of Care

Currently, there is no standard of care to prevent or treat CRCI. The most widely studied behavioral interventions, such as cognitive rehabilitation and cognitive training, require expertise to administer and are not readily available to all patients. Relatively few medications have been investigated, and even in small patient samples, results have not been encouraging. Clinical trials in psychostimulants, which do seem to improve function in certain cognitive domains, have revealed particularly poor recruitment and retention rates.[31–36] For example, methylphenidate, which to our knowledge is the only oral medication ever studied to prevent chemotherapy-related cognitive decline, failed to demonstrate adequate accrual.[34] Investigators hypothesized that this was related to stigma against the medication's established indication for childhood Attention-Deficit/Hyperactivity Disorder. The medications originally developed and currently with FDA approval for Alzheimer's disease, including donepezil and memantine, may have the most promise. They are safe, well-tolerated, with encouraging, but not conclusive, data in multi-center randomized controlled trials.[45,46,49].

1.4 Memantine

For this trial we have chosen to study the effects of memantine, an NMDA receptor antagonist. Memantine has been well studied in large population samples, including oncology populations, and shown to be safe.[49–51] It has no known drug-drug interactions with chemotherapies used for the treatment of breast cancer or medications commonly given in association with chemotherapy (e.g. ondansetron, famotidine, meperidine, epinephrine, solumedrol, dexamethasone, acetaminophen, neulasta, fosaprepitant). Memantine is partially metabolized by the liver (independent of the cytochrome p450 system) and excreted by the kidneys.

Memantine is currently only FDA approved for moderate to severe Alzheimer's disease. Glutamate, the primary excitatory neurotransmitter in the central nervous system, is thought to contribute to the pathogenesis of Alzheimer's disease by overstimulation of glutamate receptors.[47] Glutamate excess prevents magnesium ions (Mg^{2+}), which block the NMDA receptor under physiologic conditions, from re-entering the channel pore, resulting in a chronically open state. This in turn leads to excessive calcium (Ca^{2+}) influx and subsequent neuronal cell death observed in many neurodegenerative disorders.[47] Memantine binds to the intra-pore Mg^{2+} site under conditions of excessive stimulation to block the NMDA receptor and prevent cell death.[52] Chemotherapy-related cognitive decline is postulated to be a consequence of glutamate excitotoxicity as well, mediated by immune dysregulation. Specifically, peripheral levels of TNF-α are elevated in cancer, increase during chemotherapy, and are correlated with cognitive deficits.[22,53–56] Through action on neuronal TNF receptors, TNF-α increases NMDA receptor permeability to Ca^{2+} and generates excessive reactive oxygen species, resulting in neuronal death.[57] For these reasons, NMDA receptor

antagonism by memantine may be a promising approach to mitigate cognitive decline associated with chemotherapy.

Though memantine has not yet been studied for chemotherapy-related cognitive decline, there has been one clinical trial of memantine for CRCI by Brown et al. in patients receiving whole brain radiotherapy.[49] Participants were randomized to memantine or placebo, which was administered at the start of radiation and continued for 24 weeks. At baseline, 8, 16, and 24 weeks, participants underwent a neuropsychological battery (Hopkins Verbal Learning Test-Revised, HVLT-R; Trails Making Tests A and B, TMT-A, TMT-B; Controlled Oral Word Association test, COWA; and the Mini Mental Status Exam, MMSE), physical exam, brain imaging, lab tests, and evaluation of performance status. Though their primary outcome, change in HVLT-R Delayed Recall score at 24 weeks, did not reach statistical significance (p=0.059), compared to placebo memantine delayed time to overall cognitive decline and reduced the magnitude of decline in the domains of memory (HVLT-R), executive function (TMT-B), and processing speed (TMT-A) at several follow-up time points.[49] There are several clinical trials of memantine as a neuroprotective agent in the setting of cranial radiation in a variety of patient populations (adult and pediatric; primary brain tumor, brain metastases, and head and neck cancers).

1.5 Rationale for Clinical Study

An estimated 5.5 million cancer survivors in the United States suffer from CRCI,[1,2] and up to 75% of patients with cancer report cognitive deficits during active treatment.[2] On neuropsychological assessment, approximately 35% of survivors will demonstrate cognitive impairment that can last years after treatment.[2] CRCI can have profound consequences, including adverse mental health outcomes,[3,58–60] inability to return to work,[3,4] reduced quality of life,[5–7] doubled risk of dementia,[8] and increased mortality.[61]

Given that there is currently no established way to treat or prevent chemotherapy-related cognitive decline, approaches that screen for CRCI and deliver interventions that are cost-effective, available in all cancer centers, and can be easily incorporated into patient care are needed. The course of cognitive impairment resulting from cancer and its treatments are variable. However, several studies have demonstrated cognitive issues persisting years after chemotherapy that are associated with decreased gray matter volume and white matter connectivity,[21,62,63] highlighting the importance of investigating preventative approaches. Drug therapies have the potential to address the limitations of access to care seen with other CRCI interventions. There has only been one study evaluating the use of a drug to prevent CRCI, and it closed prematurely due to challenges with recruitment.[34]

In this one-arm phase II interventional study, we examine the use of memantine for CRCI prevention. In addition, the study will generate valuable information

regarding variables, including depression, anxiety, fatigue, menopausal status, sleep, estimated pre-cancer cognitive function, and self-perceived cognitive effort, that may clarify the relationship between self-reported and objectively measured cognitive function. As this is the first study investigating the use of memantine for attenuation of cognitive decline during chemotherapy, we will assess feasibility of our intervention, as measured by recruitment, retention, and adherence.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To compare changes in pre- to post-chemotherapy cognitive function, as measured by DMS score, in our cohort of patients with breast cancer receiving memantine to historical controls.

2.2 Secondary Objectives

2.2.1 To compare pre- to post-chemotherapy changes in all other objective and self-reported cognitive function measures.

2.2.2 To examine associations between objective and self-reported cognitive function with depression, anxiety, fatigue, menopausal status, baseline IQ, and perceived cognitive effort, cross-sectionally pre- and post-chemotherapy.

2.2.3 To explore the impact of cognitive decline on health-related quality of life (HRQOL), functional status, depression, and anxiety.

2.2.4 To estimate the feasibility of conducting a clinical trial of memantine for attenuating cognitive decline in patients with breast cancer during chemotherapy.

2.2.5 To describe the safety of administering memantine to patients with breast cancer during chemotherapy.

2.3 Exploratory Objectives

2.3.1 To compare pre- to 6 months post-chemotherapy changes in objective and self-reported cognitive function measures.

2.3.2 To describe changes in depression, anxiety, fatigue, HRQOL, and functional status from pre- to 6 months post-chemotherapy.

3.0 Criteria for Evaluation / Study Endpoints

3.1 Primary Endpoint

The primary endpoint is change in the pre- to post-chemotherapy DMS score. The DMS will be quantified as percent correct at 12-second delay.

3.2 Secondary Endpoints

3.2.1 Changes in other objective (HVLT-R, RVP, OTS, Digit Span, COWA, Animal Naming Test) and self-reported (PROMIS Cognitive Function) cognitive measures will be measured from pre- to post-chemotherapy.

3.2.2 Depression (PROMIS-Depression), Anxiety (PROMIS-Anxiety), fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue, FACIT-F), menopausal status (Hormonal Status Questionnaire and follicle stimulating hormone level, FSH), and perceived cognitive effort (NASA-Task Load Index, NASA-TLX) will be measured pre- and post-chemotherapy. Baseline IQ (Wechsler Adult Test of Reading, WTAR) will be measured pre-chemotherapy only.

3.2.3 Health-related quality of life (Functional Assessment of Cancer Therapy – General, FACT-G) and functional status (Patient-reported Karnofsky Performance Status, Patient-KPS) will be measured pre- and post-chemotherapy.

3.2.4 Recruitment will be measured as proportion of approached participants who agree to enroll and number of participants enrolled per month. Retention will be measured as proportion of enrolled participants who complete the primary outcome measure pre- and post-chemotherapy. Adherence will be measured as patient-reported proportion of prescribed doses of memantine actually taken.

3.2.5 Safety will be measured as the frequency of reported adverse events (AEs).

3.3 Exploratory Endpoints

3.3.1 Changes in the DMS, HVLT-R, RVP, OTS, Digit Span, COWA, Animal Naming Test, and PROMIS Cognitive function will be measured from pre- to 6 months post-chemotherapy in a subset of participants who volunteer for extended longitudinal observation.

3.3.2 Changes in PROMIS-Depression, PROMIS-Anxiety, FACIT-F, FACT-G, and Patient-KPS will be measured from pre- to 6 months post-chemotherapy in a subset of participants who volunteer for extended longitudinal observation.

4.0 PATIENT ELIGIBILITY

In order to participate in this study a participant must meet ALL of the eligibility criteria outlined below.

4.1 Inclusion Criteria

Eligible participants must meet all of the following criteria to be enrolled in the study:

4.1.1 Able to provide informed consent

4.1.2 At least 18 years of age

4.1.3 Able to speak English
4.1.4 Diagnosed with breast cancer, Stages I – III
4.1.5 Scheduled for adjuvant or neoadjuvant chemotherapy

4.2 Exclusion Criteria

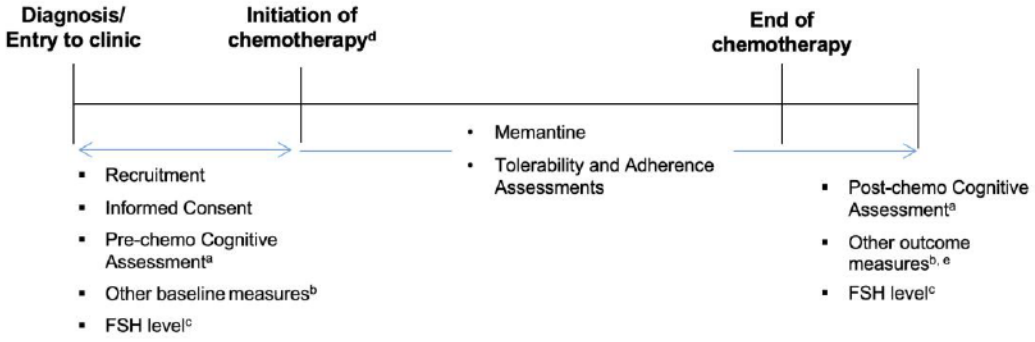
Eligible participants must not have any of the following to be enrolled in the study:

4.2.1 A history of adverse reaction to memantine
4.2.2 Another cancer diagnosis with an estimated survival of less than five years
4.2.3 Previous chemotherapy exposure
4.2.4 Severe cognitive impairment, defined as Blessed Orientation Memory Concentration Test (BOMC) ≥ 11.
4.2.5 Pregnancy, confirmed by a negative pregnancy test within 30 days of study enrollment, or breastfeeding
4.2.6 Current alcohol or drug abuse

5.0 TREATMENT PLAN

5.1 Schema

Figure 1: One arm phase II study evaluating the feasibility and efficacy of using memantine to prevent cognitive decline during adjuvant or neoadjuvant chemotherapy in patients with breast cancer



a. Objective: DMS, HVLT-R, RVP, OTS, Digit Span, COWA, ANT, BOMC, WTAR; Subjective: PROMIS Cognitive Function
b. NASA-TLX, PROMIS Depression, PROMIS Anxiety, PROMIS Sleep Disturbance, FACIT-F, KPS, FACT-G, Hormonal Status
c. Follicle-stimulating hormone level
d. TC: q3wk x 4 cycles; AC-T: q2wk x 4 cycles + taxol x 12 wk; TCH: q3wk x 6 cycles (anti-HER-2 therapy will continue beyond this point)
e. Modified Brief Medication Questionnaire-Specific

5.2 Treatment Dosage and Administration

Participants will receive memantine beginning within four weeks prior to and one week after chemotherapy initiation. All patients will be gradually titrated to 10 mg twice daily as follows: 5 mg daily in week 1, 5 mg twice daily in week 2, 5 mg each morning and 10 mg each evening in week 3, then 10 mg twice daily in week 4. Participants will continue 10 mg twice daily until 4 weeks (range: 2 to 12

weeks) after the last dose of chemotherapy. Depending on the chemotherapy regimen, total duration will range from approximately 12-30 weeks.

REGIMEN DESCRIPTION			
Agent	**Route**	**Dose**	**Schedule**
Memantine HCl	Oral	5 mg daily	Week 1
		5 mg twice daily	Week 2
		5 mg each morning, 10 mg each evening	Week 3
		10 mg twice daily	Week 4 to 4 weeks post-chemotherapy

Prescribing Information
Full prescribing information for memantine can be found at the following web address:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf

5.3 Toxicities and Dosing Delays

Any patient who receives treatment on this protocol will be evaluated by the CRA, PI, or Co-Is for toxicity. Patients will be assessed at least weekly during the titration of memantine and no less frequent than every three weeks during systemic chemotherapy. For patients receiving anti-HER2 directed therapy in addition to chemotherapy, toxicity will only be assessed during the chemotherapy segment of the regimen.

Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.

In assessing adverse events (AEs) and attribution during the course of this study, we will consider those AEs commonly associated with memantine, the specific chemotherapy administered, and chemotherapy-associated medications received.

Though all patient-reported symptoms will be recorded and examined for their association with memantine, the following most common side effects of memantine will be explicitly solicited from participants by the study team: headache, dizziness, confusion, constipation, diarrhea, and fatigue.[64] See section 6.1.7 for additional information on memantine warnings and precautions. Differentiation between memantine-associated toxicities and toxicities attributable to alternative agents will be guided by Assessing of Causality of Adverse Events outlined in 8.1.2. The treating provider will be notified of any possible, probable, or definite AEs and involved in decisions to continue, dose reduce, or stop memantine. At any time, the participant may decide to dose reduce or discontinue memantine.

If a participant experiences a grade 1 toxicity with a probable or definite attribution to memantine, the participant will remain on the same dose and symptoms will be monitored daily until the side effect is resolved.

If a participant experiences a grade 2 toxicity with a probable or definite attribution to memantine, the dose will be reduced to 5 mg PO BID (or the last tolerated dose if less) and symptoms will be monitored daily until the side effect is resolved. If no improvement, memantine will be discontinued.

If a participant experiences a grade 3 toxicity with a probable or definite attribution to memantine, the participant will discontinue memantine.

If a participant experiences toxicity with a possible attribution to memantine, the participant will remain on the same dose of memantine and symptoms will be monitored weekly until the side effect is resolved.

If a participant experiences toxicity with an unlikely or unrelated attribution to memantine, the participant will remain on the same dose and side effects will be monitored according to the scheduled outlined in the protocol (i.e., weekly during titration or no less than every 3 weeks during maintenance).

Regardless of grade or relationship with memantine, if one of the memantine side effects listed below is the reason for dose reduction of chemotherapy, the participant will reduce memantine to 5 mg PO BID (or the last tolerated dose if less) and symptoms will be monitored daily until the side effect is resolved. If no improvement, memantine will be discontinued.

- Headache
- Dizziness
- Confusion
- Constipation
- Diarrhea
- Fatigue

Regardless of whether the participant experiences any AEs, if creatinine clearance falls below 30 mL/min, the dose will also be decreased to 5 mg PO BID. If creatinine clearance falls below 5 mL/min, the study medication will be stopped.

5.4 Prohibited Medications/Treatments

There are no medications/treatments that would prohibit participants from inclusion and continued assessment in this study.

Patients on the following medications will be counseled on possible interactions with memantine and particular caution will be taken with dose escalation and side effect monitoring: drugs that may increase the serum concentration of memantine (alkalinizing agents, bupropion, carbonic anhydrase inhibitors) and drugs that

may enhance the adverse/toxic effects of memantine (trimethoprim and other NMDA receptor antagonists). Supportive medications typically used during chemotherapy for breast cancer do not have drug-drug interactions with memantine.

5.5 Duration of Therapy

Treatment will continue until 4 weeks (range 2-12 weeks) after the last dose of systemic chemotherapy or until:

- Unacceptable adverse event(s)
- Inter-current illness that prevents further administration of treatment, **OR**
- Participant decides to withdraw from the study

Decisions to remove a participant from the trial or discontinuation of treatment before planned study completion will be undertaken in conjunction with consultation from the study PI.

5.6 Duration of Follow Up

For determination of study endpoints, participants will be followed until completion of the primary endpoint (approximately 4 weeks after chemotherapy completion). A subset of participants who volunteer for extended longitudinal follow-up will be reassessed for exploratory endpoints at 6-months post-chemotherapy. All participants (including those withdrawn from protocol therapy for AEs) will be followed after removal from study treatment as stipulated in the protocol, unless the participant decides to withdraw from the study.

5.7 Study Withdrawal

Participants will be removed from protocol therapy and the PI notified when any of the criteria listed in section 5.5 apply. The reason for discontinuation of the protocol therapy will be documented on the eCRF.

If a participant decides to withdraw from the study (and not just from protocol therapy) an effort will be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the PI will attempt to establish as completely as possible the reason for the study withdrawal.

- The patient will be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet secondary objectives outlined in the protocol.
- The patient will be asked if they are willing to complete the Modified Brief Medication Questionnaire-Specific at the time of study withdrawal.
- If the reason for removal of a participant from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.8 Study Measures

Pre- and post-chemotherapy assessments will each take approximately 70 minutes to complete. An optional 10-minute break will be offered during the assessment to minimize fatigue.

OBJECTIVE COGNITIVE FUNCTION MEASURES

5.8.1 Delayed Matching to Sample Test (DMS)

The Delayed Matching to Sample Test (DMS) is a computerized cognitive assessment of visual working memory.[65,66] The DMS will be administered using CANTAB eclipse software (Cambridge Cognition, Cambridge, UK). The participant is shown an image with four patterns and asked to match patterns simultaneously or after delay. We will use the percent correct at the 12-second delay on the DMS test for the primary analysis. The DMS will take 7 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.2 Hopkins Verbal Learning Test-Revised (HVLT-R)

The HVLT-R is an objective measure of verbal learning and memory.[67] The examiner reads a list of 12 nouns to the participant, who repeats as many words as remembered. Approximately 20-25 minutes later, participants are asked to recall as many words as possible. Then, the examiner reads a list of 24 words, including the 12 words from the original list, and the participant is asked to determine which words were and were not on the original list. These tasks result in three subscales: total recall, delayed recall, and delayed recognition. The HVLT-R will take 5 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.3 Rapid Visual Information Processing (RVP)

The Rapid Visual Information Processing Test (RVP) is a computerized assessment of processing speed.[68] The RVP will be administered using CANTAB eclipse software (Cambridge Cognition, Cambridge, UK). The participant is shown a series of pseudo-random digits from 2 to 9 and asked to recognize target digit sequences by pressing a button on the screen as quickly as possible. The RVP will take 7 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.4 One Touch Stockings of Cambridge (OTS)

The One Touch Stockings of Cambridge Test (OTS) is a computerized assessment of executive function.[68] The OTS will be administered using CANTAB eclipse software (Cambridge Cognition, Cambridge, UK). The participant is shown two displays with three colored balls presented as stacks suspended from a beam and a row of numbered boxes along the bottom of the screen. In the first set of problems, the participant is asked to move the balls in the lower display to match that of the upper display. In the next set, the participant is asked to work out in their head how many moves are required to reach the

solution to each problem. The OTS will take 10 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.5 Digit Span

The Digit Span is an objective measure of attention and working memory.[69] The participant is asked to recite sequences of numbers in forward, backwards, and sequential order. The Digit Span will take 4 to 7 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.6 Controlled Oral Word Association Test (COWA)

The COWA is an objective measure of verbal fluency.[70] The participant is asked to name as many words as she can, excluding proper nouns, in one minute. This is repeated for a total for three different letters. The COWA will take 4 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.7 Animal Naming Test (ANT)

The ANT is an objective measure of semantic fluency.[71] The participant is asked to name as many animals as she can in one minute. All participants will be evaluated pre- and post-chemotherapy.

5.8.8 Wechsler Adult Test of Reading (WTAR)

The Wechsler Adult Test of Reading (WTAR) is an objective measure of intelligence quotient.[72] The participant reads 50 irregularly spelled words to provide estimated premorbid intelligence. The WTAR will take 3 minutes to complete. All participants who are enrolled in the trial will be evaluated pre-chemotherapy only.

5.8.9 Blessed Orientation Memory Concentration Test (BOMC)

The BOMC is six-item screening measure of cognitive function that assesses orientation, language, attention, concentration, and memory.[73] It has good reliability and validity[73,74] and has been incorporated into cancer-specific geriatric assessments. A score ≥ 11 has been used to suggest severe cognitive impairment. The BOMC will take less than 5 minutes to complete. All participants who are enrolled in the trial will be evaluated pre-chemotherapy.

SELF-REPORT COGNITIVE FUNCTION MEASURE

5.8.10 Modified Patient Reported Outcomes Measurement Information System – Cognitive Function (PROMIS-Cognitive Function)

The National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) contains a cognitive function bank.[75] We will use the PROMIS Cognitive Function 8a short form. Scores for all PROMIS measures are reported on the T-score metric in which the mean=50 and standard deviation (SD) = 10 are centered on the general population means. Higher scores represent

greater degrees of cognitive complaints. We will add three items to assess self-perceived pre-cancer cognitive ability and one item to explicitly assess memory. The PROMIS Cognitive Function will take less than 5 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

COVARIATES AND SECONDARY OUTCOME MEASURES

5.8.11 Modified NASA Task Load Index (NASA-TLX)

The NASA Task Load Index (NASA-TLX) is a series of single-item visual analog scales that ask participants to evaluate their performance across six domains.[76] Responses in each domain translate to a point score of 1 (lowest) to 21 (highest). For the purposes of our study, we will ask participants to self-evaluate their performance across four domains: mental demand, performance, effort, and frustration. It will be administered following each cognitive task (DMS, HVLT-R, RVP, OTS, Digit Span, COWA, ANT). The NASA-TLX will take no greater than 7 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.12 Patient Reported Outcomes Measurement Information System – Depression (PROMIS-D)

The National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) contains a depression bank.[75,77] We will use the PROMIS Depression 8a short form. Higher scores represent greater degrees of depression. The PROMIS-D will take less than 2 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.13 Patient Reported Outcomes Measurement Information System – Anxiety (PROMIS-A)

The National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) contains an anxiety bank.[75,77] We will use the PROMIS Emotional Distress-Anxiety – Short Form 6a. Higher scores represent greater degrees of anxiety. The PROMIS Anxiety will take less than 2 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.14 Patient Reported Outcomes Measurement Information System – Sleep Disturbance

The National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) contains sleep bank. We will use the PROMIS Sleep Disturbance Short Form.[75,78] Higher scores represent greater sleep difficulties. The PROMIS Sleep Disturbance Short Form will take less than 2 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.15 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The FACIT-F scale is a 13-item scale that uses a 5-point Likert-type scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much).[79] The suggested FACIT-F cut-point for significant fatigue is 36 on a 0 to 52 scale (lower scores indicating greater fatigue). The FACIT-F scale is written at the 4th grade level (Lexile framework) and takes 2-3 minutes for an average person to complete. FACIT-F will be measured pre- and post-chemotherapy.

5.8.16 Patient-Reported Karnofsky Performance Status (Patient-KPS)

The Patient-reported KPS provides a self-characterization of functional status, ranging from severely/require continuous nursing care to normal/no complaints/no symptoms of disease.[80] Scores range from 30 to 100. Higher scores indicate better function. The Patient-KPS will take less than 2 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.17 Functional Assessment of Cancer Therapy-General (FACT-G)

The FACT-G is a 27-item patient-administered assessment of general quality-of-life measures in cancer patients. It has been validated in the literature and permits the measurement of a number of symptoms including nausea, pain, and insomnia.[81] The FACT-G will take no greater than 5 minutes to complete. All participants who are enrolled in the trial will be evaluated pre- and post-chemotherapy.

5.8.18 Hormonal Status

We have developed a brief measure to assess multiple dimensions of hormonal status. Four items inquire about participants' menstrual cycles to ascertain pre-, peri-, or post-menopausal status per the Stages of Reproductive Aging Workshop + 10 (STRAW +10) criteria.[82] These items will be used in conjunction with FSH levels to clarify participants' menopausal status. Five items assess hormone sensitivity by inquiring about experiences with hormone replacement therapy, oral contraceptives, and mood changes related to menstrual cycle, pregnancy, or postpartum period. The Hormonal Status Questionnaire will take fewer than 5 minutes to complete. All participants will complete the hormonal status assessment pre- and post-chemotherapy.

5.8.19 Modified Brief Medication Questionnaire (BMQ)-Specific

The BMQ-Specific contains two five-item scales assessing patients' personal beliefs about the necessity and concerns of taking prescribed medication for their illness.[83, 84] We will use a modified version of this instrument consisting of statements specific to memantine and cognition. The Modified BMQ-Specific uses a 5-point Likert-type scale (1=strongly disagree to 5=strongly agree) to indicate participants' agreement with each statement. Total scores for the necessity and concerns scales range from 5 to 25 and are calculated by summing the individual item scores within each scale. Higher scores represent greater belief in efficacy and greater concerns, respectively. The Modified BMQ-Specific will

take fewer than 5 minutes to complete. All participants who are enrolled in the trial will be evaluated post-chemotherapy and those who withdraw will be offered to complete the assessment at the time of study withdrawal.

6.0 DRUG INFORMATION

6.1 Memantine Description and Management

6.1.1 Mechanism of Action

Memantine HCl is a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist. It binds preferentially to central nervous system NMDA receptor-operated cation channels. Additionally, memantine has antagonistic effects at the $5HT_3$ receptor and blocks nicotinic acetylcholine receptors at 10-16% potency relative to its action on NMDA and $5HT_3$ receptors.[64]

6.1.2 Indications

Memantine HCl is indicated for the treatment of moderate to severe dementia of the Alzheimer type.

6.1.3 How Supplied

The drug will be obtained from commercial supply through UNC Pharmacy and UNC Investigational Drug Service (IDS).

Full prescribing information for (Memantine HCl) is available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf

6.1.4 Dosage and Administration:

Participants will receive a gradual dose titration of memantine at 5 mg increments per week to a goal dose of 10 mg PO bid. Titration schedule is as follows:

- Week 1: 5 mg dose once daily
- Week 2: 5 mg dose twice daily
- Week 3: 5 mg each morning/10 mg each evening
- Week 4 through end of Chemotherapy: 10 mg dose twice daily

6.1.5 Storage and Stability:

Memantine HCl should be stored at room temperature (between 59° to 77° F).

6.1.6 Handling and Disposal:

Local requirements for disposal of hazardous drugs will be followed.

Please see UNC policy on hazardous drugs:
http://intranet.unchealthcare.org/intranet/hospitaldepartments/safetynet/policies/hazardousdrugs.pdf

6.1.7 Adverse Events Associated with Commercial Drug

In a meta-analysis of six phase III placebo-controlled trials of 959 patients receiving memantine HCl for moderate to severe Alzheimer's disease, the most frequently identified side effects were dizziness (6.3%), headache (5.2%), constipation (4.6%), and somnolence (3.4%).[85] The following have also been reported with the following frequencies: confusion (6%), hypertension (4%), coughing (4%), pain (3%), hallucination (3%), vomiting (3%), dyspnea (2%), and fatigue (2%).[64] A comprehensive list of adverse effects can be found at the following web address: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf

7.0 EVALUATIONS AND ASSESSMENTS

7.1 Time and Events Table

	Baseline (Pre-Chemotherapy)[a]	During Chemotherapy	Post-Chemotherapy[b]	6 Months Post-Chemotherapy[d]
Informed Consent	•			
Demographic Data Form	•			
Cancer History Form	•			
BOMC	•			
DMS	•		•	•
HVLT-R	•		•	•
RVP	•		•	•
OTS	•		•	•
Digit Span	•		•	•
COWA	•		•	•
ANT	•		•	•
WTAR	•			
Modified PROMIS-Cognitive Function	•		•	•
Modified NASA-TLX	•		•	•
PROMIS-Depression	•		•	•
PROMIS-Anxiety	•		•	•
PROMIS-Sleep Disturbance	•		•	•
Hormonal Status	•		•	•
FACIT-F	•		•	•
Patient-KPS	•		•	•
FACT-G	•		•	•
Follicle Stimulating Hormone Level	•		•[c]	
CNS-Active Medications	•	•		

Adverse Events Form		•		
Adherence		•		
Alternative CRCI treatments			•	
Modified Brief Medication Questionnaire (BMQ)-Specific			•	

a. Pre-chemotherapy assessments will occur any time between establishing care in the UNC Breast, Hillsborough Oncology, or UNC REX Cancer Center clinics and one week after the start of chemotherapy
b. Post-chemotherapy assessments will occur 4 weeks after (range: 2-12 weeks after) last dose of chemotherapy
c. FSH level will be obtained post-chemotherapy only in participants who reported still having menstrual cycles at the pre-chemotherapy assessment
d. 6-month post-chemotherapy assessments will occur only in a subset of participants who volunteer for extended longitudinal follow-up

7.2 Pre-Study (Baseline) Assessments

Patients referred to the UNC Breast Center, Hillsborough Oncology, and UNC REX Oncology clinics will be considered for enrollment in this trial. Prior to chemotherapy initiation, the CRA or PI will review the trial with the participant, confirm eligibility, and obtain informed consent. The participant will complete a cognitive assessment battery, evaluating visual working memory (DMS), verbal learning and memory (HVLT-R), processing speed (RVP), executive function (OTS), attention and working memory (Digit Span), verbal fluency (COWA), semantic fluency (ANT), and intelligence quotient (WTAR). Self-reported cognitive effort associated with each task will be evaluated using the NASA-TLX. The participant will also complete self-report assessments of cognitive function (PROMIS-Modified Cognitive Function), depression (PROMIS-D), anxiety (PROMIS-A), hormonal status, sleep (PROMIS-Sleep Disturbance), fatigue (FACIT-F), functional status (Patient-KPS), and HRQOL (FACT-G). See Appendices A – P. Follicle stimulating hormone (FSH) levels will be drawn to aid in determination of hormonal status. Following completion of all pre-study (baseline) assessments, participants will be compensated for their time with a gift card. Participants must complete all aspects of the study visit in order to receive the compensation. The CRA or investigators will also conduct a review of electronic medical records to obtain baseline information regarding medical/surgical history, the participant's cancer and cancer treatment, and demographic information. All study-related interactions will be conducted in private rooms at UNC Breast, Hillsborough Oncology, and UNC REX Cancer Center clinics; in private rooms at participants' homes; over the phone; and by video conferencing after confirming that subjects are in a private location. Study assessments and questionnaires will be offered by email and mail as is necessary and feasible.

7.3 Treatment

If the participant meets all inclusion/exclusion criteria and provides informed consent, she will receive memantine beginning within four weeks before and one week after chemotherapy initiation until the post-chemotherapy assessment, approximately four weeks after the last dose of chemotherapy (estimated total duration of memantine: 12-30 weeks). Tolerability of memantine and medication adherence will be serially assessed for the duration of treatment. Patients will be assessed at an interval no greater than every three weeks. For patients receiving anit-HER2 directed therapy in addition to chemotherapy, toxicity will only be assessed during the chemotherapy segment of the regimen. Tolerability will be assessed as described in section 5.3. Medication adherence will be tracked using number of patient-estimated missed doses since last assessment.

7.4 Post-Chemotherapy Assessment

The participant will complete a post-chemotherapy assessment approximately 4 weeks after the end of chemotherapy (range: 2 to 12 weeks post-chemotherapy). The CRA will meet with the participant to complete a cognitive assessment for visual working memory (DMS), verbal learning and memory (HVLT-R), processing speed (RVP), executive function (OTS), attention and working memory (Digit Span), verbal fluency (COWA), and semantic fluency (ANT). The participant will also complete self-report assessments for cognitive function (PROMIS-Modified Cognitive Function), cognitive effort (NASA-TLX), depression (PROMIS-D), anxiety (PROMIS-Anxiety), sleep disturbance (PROMIS-Sleep Disturbance), fatigue (FACIT-F), functional status (KPS), hormonal status, HRQOL (FACT-G), and beliefs about the necessity and concerns of taking memantine (Modified BMQ-Specific). See Appendices A – Q. In participants who were not classified as post-menopausal at study entry, FSH levels will be drawn. The participants will also be asked if they engaged in any other activities or received medications during the study period that they believe preserved their cognitive function. When assessments cannot be completed, this will be noted in the eCRF. Following completion of all post-chemotherapy assessments, participants will be compensated for their time with a gift card. Participants must complete all aspects of the study visit in order to receive the compensation. As with the pre-chemotherapy assessment, the post-chemotherapy assessment will be conducted in private rooms at UNC Breast, Hillsborough Oncology, and UNC REX Cancer Center clinics; in private rooms at participants' homes; over the phone; and by video conferencing after confirming that subjects are in a private location. The post-chemotherapy assessment and questionnaires will be offered by email and mail as is necessary and feasible.

7.5 6-Month Post-Chemotherapy Assessment (subset only)

Participants who at the time of initial consent indicate interest in being observed over extended longitudinal follow-up will complete an additional assessment 6 months after completing chemotherapy (range: 4 to 8 months post-chemotherapy). The CRA will meet with the participant to complete a cognitive assessment for

visual working memory (DMS), verbal learning and memory (HVLT-R), processing speed (RVP), executive function (OTS), attention and working memory (Digit Span), verbal fluency (COWA), and semantic fluency (ANT). The participant will also complete self-report assessments for cognitive function (PROMIS-Modified Cognitive Function), cognitive effort (NASA-TLX), depression (PROMIS-D), anxiety (PROMIS-Anxiety), sleep disturbance (PROMIS-Sleep Disturbance), fatigue (FACIT-F), functional status (KPS), hormonal status, and HRQOL (FACT-G). See Appendices A – P. Following completion of all post-chemotherapy assessments, participants will be compensated for their time with a gift card. Participants must complete all aspects of this study visit in order to receive the compensation. As with the pre-and post-chemotherapy assessments, this will be conducted in private rooms at UNC Breast, Hillsborough Oncology, and UNC REX Cancer Center clinics; in private rooms at participants' homes; over the phone; and by video conferencing after confirming that subjects are in a private location. The post-chemotherapy assessment and questionnaires will be offered by email and mail as is necessary and feasible.

7.6 Concurrent CNS Active Medications

All concurrent CNS active medications, including psychostimulants, acetylcholinesterase inhibitors, other NMDA receptor antagonists, antidepressants, anxiolytics, antipsychotics, antiepileptics, and antihistamines will be documented at Baseline/Screening and throughout the study as summarized in the Time and Events Table in Section 7.1.

7.7 Demographics

Demographic information (date of birth, gender, race, educational level) will be recorded by the CRA from review of medical records at baseline.

7.8 Medical History

Relevant medical history, including history of current disease, and information regarding underlying diseases will be abstracted from medical records at baseline.

7.9 Handling of Biospecimens Collected for Correlative Research

Biospecimens for this study will be collected by a certified phlebotomist and stored in the Lineberger Comprehensive Cancer Center (LCCC) associated laboratory. Each sample will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Researchers with IRB-approval for access to PHI for each participant in this study will be able to link specimens to relevant medical information.

Storage Time:

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the patient to use her blood for other research purposes (e.g., consent form was signed by the patient). In this circumstance, biospecimens may be stored for no longer than 15 years.

Compliance Statement
Biospecimen collection for this study will be conducted in full accordance with all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research participants during and after the study.

7.10 Assessment of Safety

Any patient who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each patient will be assessed at least weekly during the titration of memantine and no less frequent than every three weeks during systemic chemotherapy for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAE version 5.

7.11 Assessment of Efficacy

All participants who enroll, receive at least one dose of study medication, and complete the primary outcome measure will be analyzed.

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE.

8.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

Assessing Causality of Adverse Events

The likelihood of causality of all AE's will be graded as described below. Given that potential side effects of memantine overlap with those due to chemotherapy (and many other medications), we will consider not only the presence/absence of the AE, but also worsening in the severity or frequency of the AE in assessing causality.

Unrelated: Adverse event and/or its severity or frequency are clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2): Adverse event and/or its severity or frequency:
1. does not have temporal relationship to intervention
2. could not readily have been produced by the participant's clinical state

3. could have been due to environmental or other interventions
4. does not follow a known pattern of response to intervention
5. does not reappear or worsen with reintroduction of intervention

Possible (must have 2): Adverse event and/or its severity or frequency:
1. has a reasonable temporal relationship to intervention
2. could not readily have been produced by the participant's clinical state
3. could not have been due to environmental or other interventions
4. follows a known pattern of response to intervention

Probable (must have 3): Adverse Event and/or its severity or frequency:
1. has a reasonable temporal relationship to intervention
2. could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
3. follows a known pattern of response to intervention
4. disappears or decreases with reduction in dose or cessation of intervention

Definite (must have all 4): Adverse Event and/or its severity or frequency:
1. has a reasonable temporal relationship to intervention
2. could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
3. follows a known pattern of response to intervention
4. disappears or decreases with reduction in dose or cessation of intervention

8.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- 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 patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

8.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

8.3 SAEs or Serious SARs

8.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

8.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the NCCN Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

8.4 Adverse Event Reporting

8.4.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 10.4.3) within 7 days of the Investigator becoming aware of the problem.

8.4.2 Funding Source (e.g. Manufacturer) Reporting Requirements:

N/A

8.5 Data and Safety Monitoring Plan

This is a Phase II, single site study of 56 individuals to gather preliminary data on the efficacy and feasibility of memantine in patients with breast cancer receiving chemotherapy. We will follow our standard protocol for monitoring of clinical trials. Participants are screened to ensure that there are no contraindications to their participation.

The study PI, Dr. Nakamura, will be responsible for continuous monitoring of patient safety during the trial. For non-serious Adverse Events (AEs), documentation will begin from the first day of study treatment and continue through the 30-day follow-up period after treatment is discontinued. Collected information will be recorded in Case Report Forms (CRF) for that patient. A description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug will be included. For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event will begin after signing of the informed consent and continue through the 30-day follow-up period after treatment is discontinued. These events will be recorded in the CRF for that patient within 24 hours of learning of its occurrence. If the event is both serious AND unexpected, it will also be recorded on the MedWatch Form 3500A, as per 21 CFR 312.32, and forwarded to the FDA in accordance with 21 CFR 314.80 (for marketed drugs). The UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem (serious, unexpected, and related) as per the UNC IRB policies. In accordance with these policies, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal.

Periodic review, at an interval of every six months to annually, by the Lineberger Comprehensive Cancer Center Data Safety Committee (LCCC DSMC), Protocol Review Committee (PRC), and Office of Human Research Ethics (OHRE) Biomedical IRB will provide oversight of the PI's continuous monitoring. For each DSMC review, summary information regarding toxicity and accrual patterns will be prepared and submitted by the PI. Specific information submitted for review includes: (1) The number of patients enrolled, consented, consented but not treated, currently being treated, completed treatment, the number of patients who did not complete treatment and the reasons for coming off study; (2) Grade 3 or greater reported Adverse Events to date; (3) Serious

Adverse Events and Unanticipated Problems since last report, with assurance of reporting to internal and external regulating bodies; (4) Exceptions in eligibility or treatment and significant protocol deviations/violations; (5) Significant literature reporting developments that may affect the safety of participants or the ethics of the study; (6) Summaries of team meetings that have occurred since the last report; (7) Results of interim analyses required by the protocol. We will also be submitting a preliminary report of response and other endpoints listed in the primary and secondary objectives of the protocol for DSMC review.

Though no formal *a priori* stopping rules are proposed for the study, in the event of a serious or unexpected adverse event or frequent occurrence of less serious unexpected or expected adverse events we will consult with the OHRE and DSMC as to whether the trial should continue.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

This is a one-arm interventional pilot study in participants receiving chemotherapy for breast cancer to evaluate if memantine can prevent cognitive decline. We will recruit 56 patients from the UNC Breast, Hillsborough Oncology, and UNC REX Cancer Center clinics, treat with memantine 10 mg twice daily, and systematically evaluate cognitive function, mental health, HRQOL, and functional status at baseline and at the end of chemotherapy (and again at 6 months post-chemotherapy in a subset of participants). We will also serially assess tolerability of and adherence with memantine.

The primary efficacy endpoint is cognitive decline measured as a change in DMS score. Scores range from 0-100%, defined by the percent of correct answers on the memory test. Secondary endpoints include other measures of cognitive function (HVLT-R, RVP, OTS, Digit Span, COWA, ANT, and PROMIS Cognitive Function), depression, anxiety, HRQOL, and functional status. The TMT-A and -B will also be evaluated as secondary endpoints in the subset of participants who completed the study prior to the removal of these measures.

9.2 Sample Size, Accrual and Duration of Accrual

Though chemotherapy is known to result in cognitive decline, the study by Janelsins reports a 5% increase in scores on the DMS (83% to 88%) in patients with breast cancer from pre-to post-chemotherapy.[68] An increase in score in spite of cognitive decline is consistent with the well-described phenomena of practice effects in both healthy and cancer populations with repeat neuropsychological testing.[86] In our sample exposed to memantine, we hypothesize that our sample will have an 8% increase in the DMS score as compared to the 5% increase in breast cancer controls described in Janelsins study.

For the primary objective of cognitive change, a paired t-test with a 0.05 one-sided significance level will have 80% power to detect an effect size of 0.376 with a sample size of 45. Specifically, patients with breast cancer demonstrate a 5% increase in the DMS pre- to post- chemotherapy;[68] thus, 5% is the null hypothesized change. The alternative hypothesis is that patients receiving memantine will experience less chemotherapy-related cognitive decline, and will have an 8% increase. Using these hypothesized values, in combination with sample size budgetary constraints, we chose the final sample size of 45. With 45 patients, we will have 80% power to test if the change scores in our study population are significantly different than the historical control data reported by Janelsins (assuming a 3% mean increase, and standard deviation of the increase of 7.97%). This study will provide preliminary data and effect sizes to power a future, larger placebo-controlled study.

To account for dropout of up to 20%, we will enroll 56 participants. The UNC Cancer Registry records demonstrate that 537 stage I-III breast cancer patients were referred to the NC Cancer Hospital for chemotherapy between 2016 and 2017. We estimate that we will enroll at least 33% of eligible participants, based on our experience with previous intervention studies, allowing us to recruit our target within one year.

9.3 Data Analysis Plans

The primary outcome is change in the DMS score. A paired t-test will test if the change in DMS score from pre- to post-chemotherapy is statistically different from historical controls. Pre- to post-chemotherapy, as well as pre- to 6 months post-chemotherapy, changes in all other cognitive measures will also be evaluated using paired t-tests.

Linear regression models will be used to cross-sectionally evaluate associations between depression (PROMIS-D), anxiety (PROMIS-A), sleep (PROMIS-Sleep Disturbance), menopausal status, fatigue (FACIT-F), estimated pre-cancer IQ (WTAR), and cognitive effort (NASA-TLX) with both objective (DMS, HVLT-R, COWA, ANT, Digit Span) and self-reported (PROMIS) measures of cognitive function at baseline and post-chemotherapy. Linear mixed effects models will evaluate associations across pre- and post- time points.

Linear regression modeling will describe the associations between pre- to post-chemotherapy cognitive changes (DMS, HVLT-R, COWA, ANT, Digit Span, PROMIS) with post-chemotherapy depression and anxiety (PROMIS), HRQOL (FACT-G), and performance status (KPS).

Descriptive statistics will be used to estimate feasibility: 1.) recruitment rate (% of invited participants who enroll), 2.) attrition (% of enrolled participants who are not eligible for analysis of the primary outcome), and 3.) adherence to treatment (% self-reported doses of memantine taken).

We will tabulate all AEs, the dose at which they occurred, and if they led to dosing delays or removal from the study.

10.0 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

10.3 Registration Procedures

Patient enrollment in the study will be tracked in OnCore®. This will allow the UNC Lineberger Comprehensive Cancer Center to track accrual into the study. For all potentially eligible and interested patients, eligibility criteria must be confirmed prior to registration by the PI.

10.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

10.4.2 Single Patient/Participant Exceptions

Any request to enroll a single participant who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

10.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems: Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

10.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

10.6 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study

staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 REFERENCES

1. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016;
2. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. Int Rev Psychiatry. 2014;26(1):102–13.
3. Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers CA. "Chemobrain" in breast carcinoma?: a prologue. Cancer. 2004 Aug;101(3):466–75.
4. Bradley CJ, Neumark D, Luo Z, Bednarek H, Schenk M. Employment outcomes of men treated for prostate cancer. J Natl Cancer Inst. 2005 Jul;97(13):958–65.
5. Mehnert A, Scherwath A, Schirmer L, Schleimer B, Petersen C, Schulz-Kindermann F, et al. The association between neuropsychological impairment, self-perceived cognitive deficits, fatigue and health related quality of life in breast cancer survivors following standard adjuvant versus high-dose chemotherapy. Patient Educ Couns. 2007 Apr;66(1):108–18.
6. Myers SB, Manne SL, Kissane DW, Ozga M, Kashy DA, Rubin S, et al. Social-cognitive processes associated with fear of recurrence among women newly diagnosed with gynecological cancers. Gynecol Oncol. 2013 Jan;128(1):120–7.
7. Von Ah D, Russell KM, Storniolo AM, Carpenter JS. Cognitive Dysfunction and Its Relationship to Quality of Life in Breast Cancer Survivors. Oncol Nurs Forum. 2009 May;36(3):326–36.
8. Heflin LH, Meyerowitz BE, Hall P, Lichtenstein P, Johansson B, Pedersen NL, et al. Cancer as a risk factor for long-term cognitive deficits and dementia. J Natl Cancer Inst. 2005;97(11):854–6.
9. Cherrier MM, Anderson K, David D, Higano CS, Gray H, Church A, et al. A randomized trial of cognitive rehabilitation in cancer survivors. Life Sci. 2013 Oct;93(17):617–22.
10. Ercoli LM, Castellon SA, Hunter AM, Kwan L, Kahn-Mills BA, Cernin PA, et al. Assessment of the feasibility of a rehabilitation intervention program for breast cancer survivors with cognitive complaints. Brain Imaging Behav. 2013 Dec;7(4):543–53.
11. Schuurs A, Green HJ. A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. Psychooncology. 2013 May;22(5):1043–9.
12. Zimmer P, Baumann FT, Oberste M, Wright P, Garthe A, Schenk A, et al. Effects of exercise interventions and physical activity behavior on cancer related cognitive impairments: A systematic review. Vol. 2016, BioMed Research International. 2016.
13. Ehlers DK, Aguiñaga S, Cosman J, Severson J, Kramer AF, McAuley E. The effects of physical activity and fatigue on cognitive performance in breast cancer survivors. Breast Cancer Res Treat. 2017;165(3):699–707.
14. Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and

endocrine-related quality of life, and well-being in stage 0 to III breast cancer: A randomized, controlled trial. J Clin Oncol. 2012;30(12):1335–42.

15. Milbury K, Chaoul A, Biegler K, Wangyal T, Spelman A, Meyers CA, et al. Tibetan sound meditation for cognitive dysfunction: Results of a randomized controlled pilot trial. Psychooncology. 2013;22(10):2354–63.
16. Johns SA, Brown LF, Beck-Coon K, Talib TL, Monahan PO, Giesler RB, et al. Randomized controlled pilot trial of mindfulness-based stress reduction compared to psychoeducational support for persistently fatigued breast and colorectal cancer survivors. Support Care Cancer. 2016;24(10):4085–96.
17. Abraham J, Haut MW, Moran MT, Filburn S, Lemiuex S, Kuwabara H. Adjuvant chemotherapy for breast cancer: effects on cerebral white matter seen in diffusion tensor imaging. Clin Breast Cancer. 2008 Feb;8(1):88–91.
18. de Ruiter MB, Reneman L, Boogerd W, Veltman DJ, Caan M, Douaud G, et al. Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: converging results from multimodal magnetic resonance imaging. Hum Brain Mapp. 2012 Dec;33(12):2971–83.
19. Jung MS, Zhang M, Askren MK, Berman MG, Peltier S, Hayes DF, et al. Cognitive dysfunction and symptom burden in women treated for breast cancer: a prospective behavioral and fMRI analysis. Brain Imaging Behav. 2017;11(1):86–97.
20. Conroy SK, McDonald BC, Smith DJ, Moser LR, West JD, Kamendulis LM, et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Cancer Res Treat. 2013 Jan;137(2):493–502.
21. Inagaki M, Yoshikawa E, Matsuoka Y, Sugawara Y, Nakano T, Akechi T, et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. Cancer. 2007 Jan;109(1):146–56.
22. Kesler S, Janelsins M, Koovakkattu D, Palesh O, Mustian K, Morrow G, et al. Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain Behav Immun. 2013 Mar;30 Suppl:S109-16.
23. Jenkins V, Shilling V, Deutsch G, Bloomfield D, Morris R, Allan S, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer. 2006;94(6):828–34.
24. Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. J Clin Exp Neuropsychol. 2004;26(7):955–69.
25. Shilling V, Jenkins V. Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. Eur J Oncol Nurs. 2007;11(1):6–15.
26. Shilling V, Jenkins V, Morris R, Deutsch G, Bloomfield D. The effects of adjuvant chemotherapy on cognition in women with breast cancer - Preliminary results of an observational longitudinal study. Breast. 2005;
27. Van Dam FSAM, Schagen SB, Muller MJ, Boogerd W, V.D. Wall E, Droogleever Fortuyn ME, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: High-dose versus standard-dose

chemotherapy. J Natl Cancer Inst. 1998;

28. Bender CM, Pacella ML, Sereika SM, Brufsky AM, Vogel VG, Rastogi P, et al. What do perceived cognitive problems reflect? J Support Oncol. 2008;6(5):238–42.
29. Downie FP, Mar Fan HG, Houédé-Tchen N, Yi Q, Tannock IF. Cognitive function, fatique, and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: Evaluation with patient interview after formal assessment. Psychooncology. 2006;15(10):921–30.
30. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011 Jul;12(7):703–8.
31. Gehring K, Patwardhan SY, Collins R, Groves MD, Etzel CJ, Meyers CA, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. J Neurooncol. 2012;107(1):165–74.
32. Boele FW, Douw L, De Groot M, Van Thuijl HF, Cleijne W, Heimans JJ, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: A multicenter randomized controlled trial. Neuro Oncol. 2013;15(10):1420–8.
33. Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol [Internet]. 1998;16(7):2522–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9667273
34. Mar Fan HG, Clemons M, Xu W, Chemerynsky I, Breunis H, Braganza S, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. Support Care Cancer [Internet]. 2008;16(6):577–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17972110
35. Kohli S, Fisher SG, Tra Y, Jacob Adams M, Mapstone ME, Wesnes KA, et al. The effect of modafinil on cognitive function in breast cancer survivors. Cancer. 2009;115(12):2605–16.
36. Lundorff LE, Jønsson BH, Sjøgren P. Modafinil for attentional and psychomotor dysfunction in advanced cancer: A double-blind, randomised, cross-over trial. Palliat Med. 2009;23(8):731–8.
37. Barton DL, Burger K, Novotny PJ, Fitch TR, Kohli S, Soori G, et al. The use of Ginkgo biloba for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9. Support Care Cancer. 2013;21(4):1185–92.
38. Chan AS, Cheung MC, Law SC, Chan JH. Phase II Study of Alpha-Tocopherol in Improving the Cognitive Function of Patients with Temporal Lobe Radionecrosis. Cancer. 2004;
39. Chang J, Couture FA, Young SD, Lau CY, Lee McWatters K. Weekly Administration of Epoetin Alfa Improves Cognition and Quality of Life in Patients with Breast Cancer Receiving Chemotherapy. Support Cancer Ther [Internet]. 2004;2(1):52–8. Available from:

http://linkinghub.elsevier.com/retrieve/pii/S1543291213601083

40. O'Shaughnessy JA, Vukelja SJ, Holmes FA, Savin M, Jones M, Royall D, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. Clin Breast Cancer. 2005;5(6):439–46.
41. O'Shaughnessy J a. Effects of epoetin alfa on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant chemotherapy. Clin Breast Cancer [Internet]. 2002;3 Suppl 3(December):S116–20. Available from: http://dx.doi.org/10.3816/CBC.2002.s.022
42. Iconomou G, Koutras a, Karaivazoglou K, Kalliolias GD, Assimakopoulos K, Argyriou a a, et al. Effect of epoetin alpha therapy on cognitive function in anaemic patients with solid tumours undergoing chemotherapy. Eur J Cancer Care (Engl) [Internet]. 2008;17(6):535–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18707621
43. Massa E, Madeddu C, Lusso MR, Gramignano G, Mantovani G. Evaluation of the effectiveness of treatment with erythropoietin on anemia, cognitive functioning and functions studied by comprehensive geriatric assessment in elderly cancer patients with anemia related to cancer chemotherapy. Crit Rev Oncol Hematol. 2006 Feb;57(2):175–82.
44. Administration USF and D. FDA drug safety communication: Erythropoiesis-stimulating agents (ESAs): Procrit, Epogen and Aranesp. [Internet]. 2011. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm
45. Lawrence JA, Griffin L, Balcueva EP, Groteluschen DL, Samuel TA, Lesser GJ, et al. A study of donepezil in female breast cancer survivors with self-reported cognitive dysfunction 1 to 5 years following adjuvant chemotherapy. J Cancer Surviv. 2015;
46. Rapp SR, Case LD, Peiffer A, Naughton MM, Chan MD, Stieber VW, et al. Donepezil for irradiated brain tumor survivors: A phase III randomized placebo-controlled clinical trial. J Clin Oncol. 2015;33(15):1653–9.
47. Zou JY, Crews FT. TNFα potentiates glutamate neurotoxicity by inhibiting glutamate uptake in organotypic brain slice cultures: Neuroprotection by NFκB inhibition. Brain Res. 2005;1034(1–2):11–24.
48. Floden AM, Li S, Combs CK. Beta-amyloid-stimulated microglia induce neuron death via synergistic stimulation of tumor necrosis factor alpha and NMDA receptors. J Neurosci [Internet]. 2005;25(10):2566–75. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15758166%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/15758166
49. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15(10):1429–37.
50. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. In: Cochrane Database of Systematic Reviews [Internet]. 2006. Available from:

http://doi.wiley.com/10.1002/14651858.CD003154.pub5

51. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in Moderate-to-Severe Alzheimer's Disease. N Engl J Med [Internet]. 2003;348(14):1333–41. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa013128
52. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. Nat Rev Drug Discov. 2006;5(2):160.
53. Pomykala KL, Ganz PA, Bower JE, Kwan L, Castellon SA, Mallam S, et al. The association between pro-inflammatory cytokines, regional cerebral metabolism, and cognitive complaints following adjuvant chemotherapy for breast cancer. Brain Imaging Behav. 2013 Dec;7(4):511–23.
54. Ganz PA, Bower JE, Kwan L, Castellon SA, Silverman DHS, Geist C, et al. Does tumor necrosis factor-alpha (TNF-alpha) play a role in post-chemotherapy cerebral dysfunction? Brain Behav Immun. 2013 Mar;30 Suppl:S99-108.
55. Patel SK, Wong AL, Wong FL, Breen EC, Hurria A, Smith M, et al. Inflammatory Biomarkers, Comorbidity, and Neurocognition in Women With Newly Diagnosed Breast Cancer. J Natl Cancer Inst. 2015 Aug;107(8).
56. Wang XM, Walitt B, Saligan L, Tiwari AFY, Cheung CW, Zhang ZJ. Chemobrain: A critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. Vol. 72, Cytokine. 2015. p. 86–96.
57. Olmos G, Llado J. Tumor necrosis factor alpha: a link between neuroinflammation and excitotoxicity. Mediators Inflamm. 2014;2014:861231.
58. Oh P-J. Predictors of cognitive decline in people with cancer undergoing chemotherapy. Eur J Oncol Nurs Off J Eur Oncol Nurs Soc. 2017 Apr;27:53–9.
59. Bender CM, Sereika SM, Berga SL, Vogel VG, Brufsky AM, Paraska KK, et al. Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology. 2006 May;15(5):422–30.
60. Schagen SB, Muller MJ, Boogerd W, Rosenbrand RM, van Rhijn D, Rodenhuis S, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Ann Oncol Off J Eur Soc Med Oncol. 2002 Sep;13(9):1387–97.
61. Hshieh TT, Jung WF, Grande LJ, Chen J, Stone RM, Soiffer RJ, et al. Prevalence of cognitive impairment and association with survival among older patients with hematologic cancers. JAMA Oncol. 2018;4(5):686–93.
62. Janelsins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. Semin Oncol. 2011 Jun;38(3):431–8.
63. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin. 2015 Mar;65(2):123–38.
64. Memantine Prescribing Information. 2013.
65. Fray PJ, Robbins TW. CANTAB battery: Proposed utility in neurotoxicology. In: Neurotoxicology and Teratology. 1996.
66. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor

analytic study of a large sample of normal elderly volunteers. Dementia. 1994;5(5):266–81.

67. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. Clin Neuropsychol [Internet]. 1998;12(1):43–55. Available from: http://www.ingentaconnect.com/content/psych/clin/1999/00000013/00000003/art00010
68. Janelsins MC, Heckler CE, Peppone LJ, Ahles TA, Mohile SG, Mustian KM, et al. Longitudinal Trajectory and Characterization of Cancer-Related Cognitive Impairment in a Nationwide Cohort Study. J Clin Oncol. 2018 Sep;JCO2018786624.
69. Wechsler D. Manual for the Wechsler adult intelligence scale-revised (WAIS-R). San Antonio, TX Psychol Corp. 1981;
70. Bechtoldt HP, Benton AL, Fogel ML. An application of factor analysis in neuropsychology. Psychol Rec [Internet]. 1962 Apr;12(2):147–56. Available from: https://doi.org/10.1007/BF03393452
71. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999;14(2):167–77.
72. Wechsler D. Wechsler Test of Adult Reading: WTAR. Psychological Corporation; 2001.
73. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry. 1983 Jun;140(6):734–9.
74. Wade DT, Vergis E. The Short Orientation–Memory–Concentration Test: a study of its reliability and validity. Clin Rehabil. 1999;13(2):164–70.
75. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol [Internet]. 2010;63(11):1179–94. Available from: http://www.sciencedirect.com/science/article/pii/S0895435610001733
76. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research. Adv Psychol. 1988;
77. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment. 2011 Sep;18(3):263–83.
78. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment. 2011 Sep;18(3):263–83.
79. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer. 2002;94(2):528–38.
80. Loprinzi CL, Laurie JA, Wieand HS, Krook JE, Novotny PJ, Kugler JW, et al. Prospective evaluation of prognostic variables from patient-completed

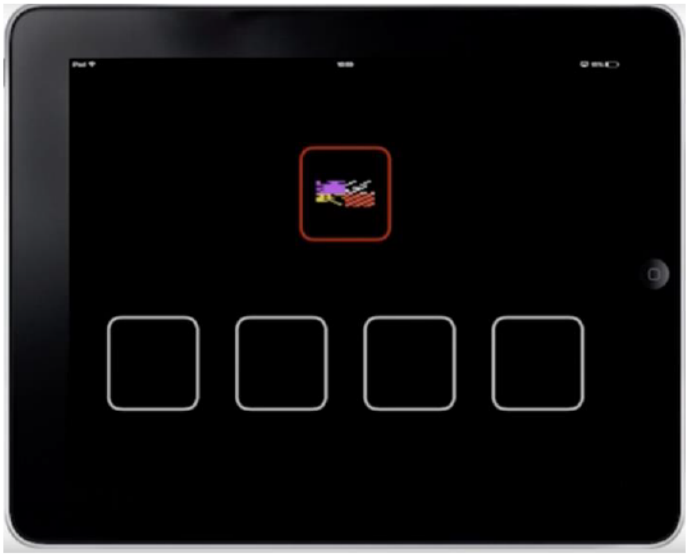
questionnaires. North Central Cancer Treatment Group. J Clin Oncol [Internet]. 1994;12(3):601–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8120560

81. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570–9.
82. Group for the S+ 10 C, Harlow SD, Gass M, Hall JE, Lobo R, Maki P, et al. Executive Summary of the Stages of Reproductive Aging Workshop + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. J Clin Endocrinol Metab [Internet]. 2012 Apr 1;97(4):1159–68. Available from: https://doi.org/10.1210/jc.2011-3362
83. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res. 1999;47(6):555–67.
84. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1–24.
85. B. W, R.W. J, Y. W, A. S, H.J. M. Memantine in moderate to severe alzheimer's disease: A meta-analysis of randomised clinical trials. Dementia and Geriatric Cognitive Disorders. 2007.
86. Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB. Cancer and cancer-therapy related cognitive dysfunction: An international perspective from the Venice cognitive workshop. Annals of Oncology. 2008.

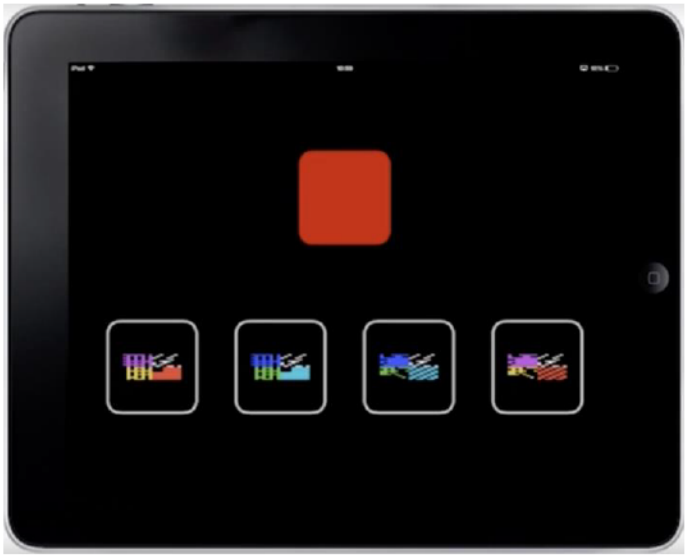
12.0 APPENDICES

Appendix A: Delayed Matching to Sample Test (DMS)

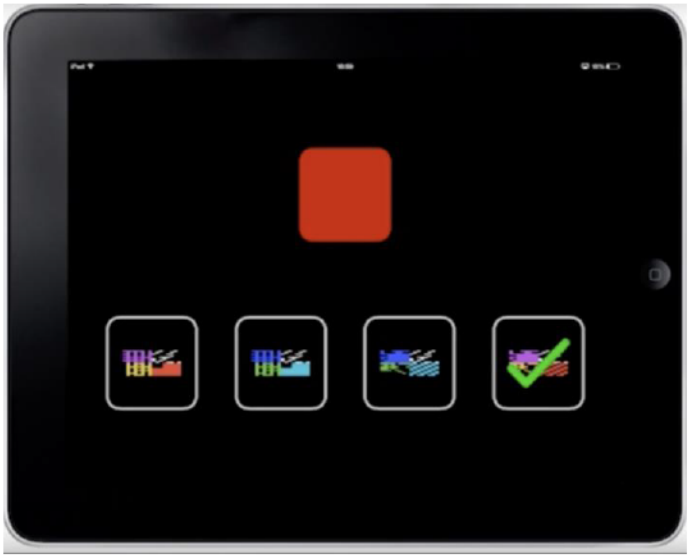
The participant is shown a complex visual image.



The image is hidden from the participant, and the participant is shown four similar images simultaneously or after a 4- or 12-second delay.



The participant must select the image that exactly matches the sample.



Appendix B: Rapid Visual Information Processing (RVP)

The participant is asked to recognize a target digit sequence out of a series of pseudo-random digits from 2 to 9.

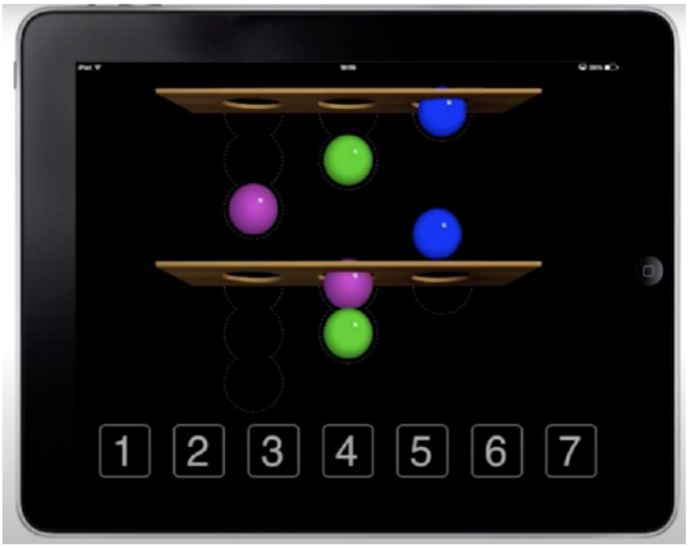
The participant presses a button on the bottom of the screen as quickly as possible after they recognize the target digit sequence.


5
3 · 5 · 7

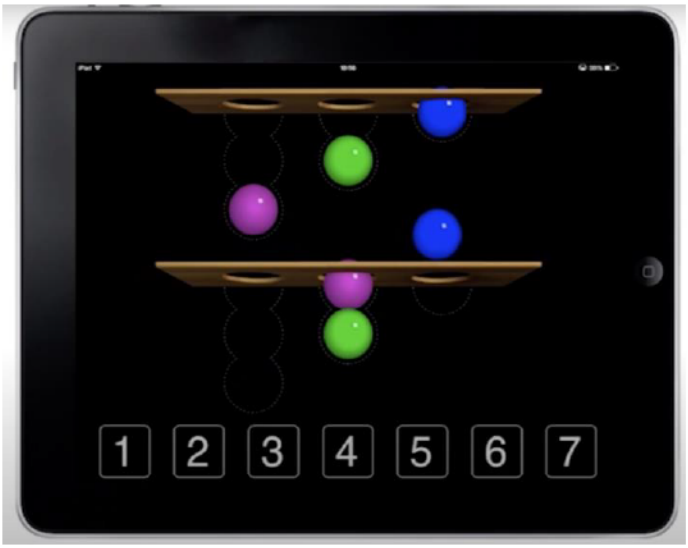

7
3 · 5 · 7

Appendix C: One Touch Stockings of Cambridge (OTS)

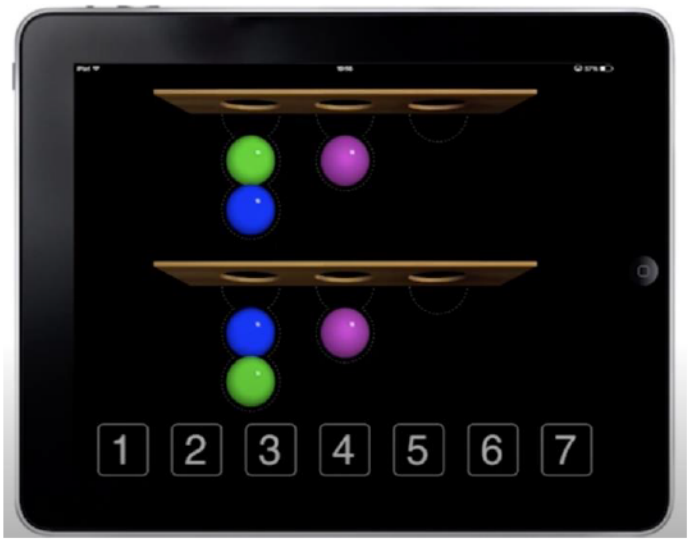
The participant is shown two displays with three colored balls presented as stacks suspended from a beam and a row of numbered boxes along the bottom of the screen.



In the first set of problems, the participant is asked to move the balls in the lower display to match that of the upper display.



Then, the participant is shown additional problems and asked to work out in her head how many moves are required to reach the solution.



Appendix D: Hopkins Verbal Learning Test-Revised (HVLT-R)

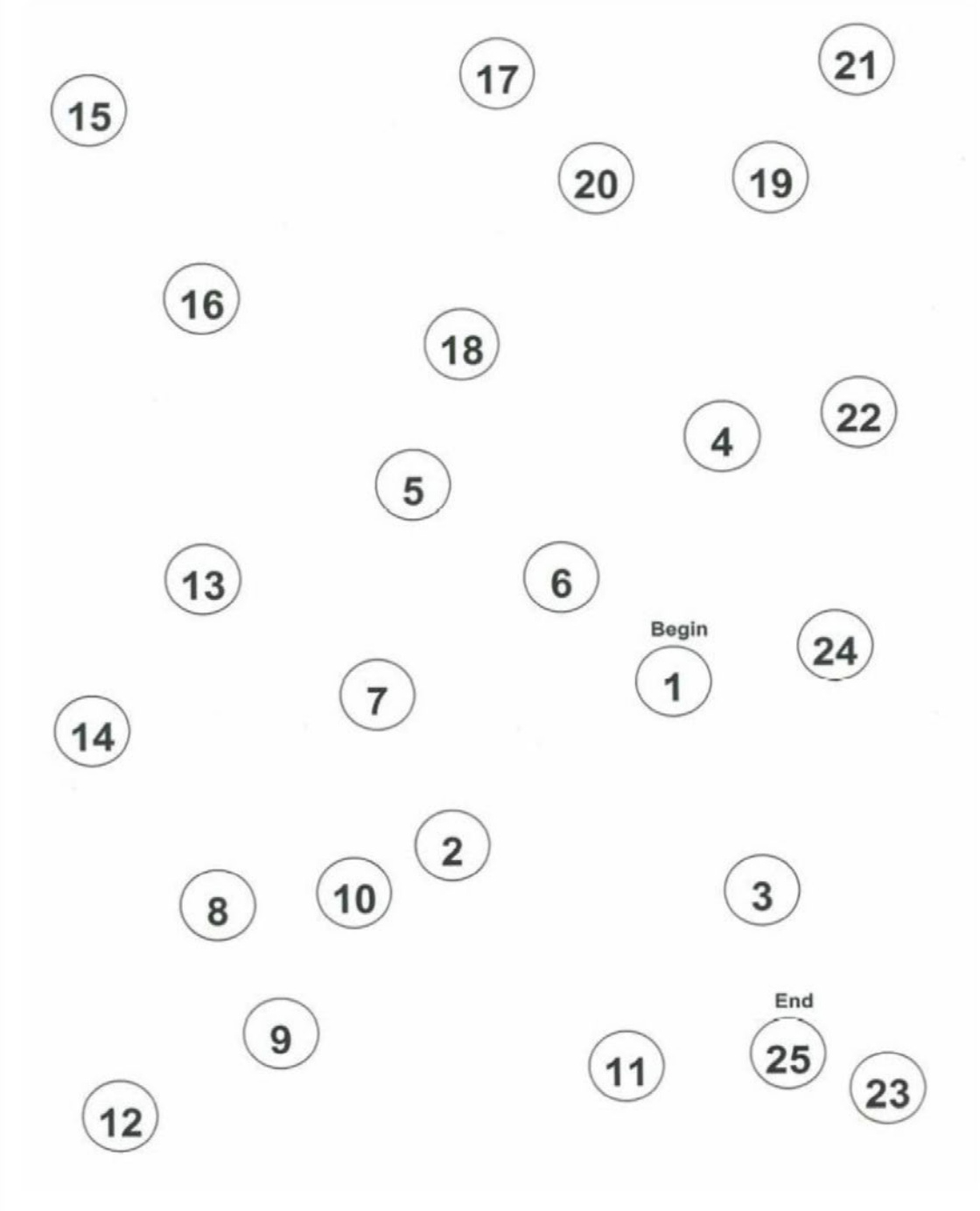
Word List	Learning Trials			Delayed Recall Trial (20-25 min.)
	Trial 1	Trial 2	Trial 3	Trial 4
LION				
EMERALD				
HORSE				
TENT				
SAPPHIRE				
HOTEL				
CAVE				
OPAL				
TIGER				
PEARL				
COW				
HUT				
Total correct responses =				

Completion Time Trial 3 _____ Start Time Trial 4 _____

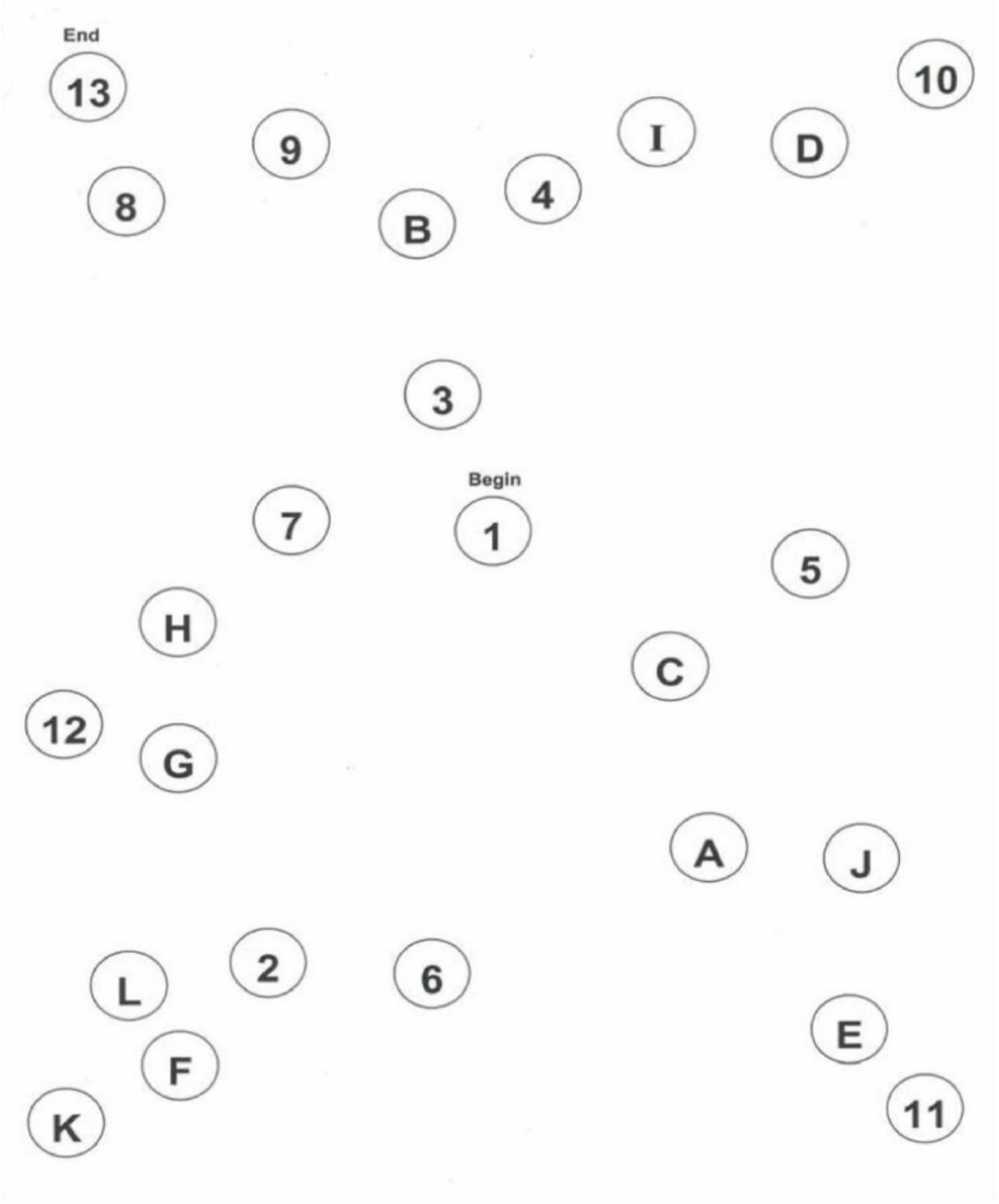
Delayed Recognition Trial (Forced Choice)			
1. HORSE Y N	7. house Y N	13. HUT Y N	19. TENT Y N
2. ruby Y N	8. OPAL Y N	14. EMERALD Y N	20. mountain Y N
3. CAVE Y N	9. TIGER Y N	15. SAPPHIRE Y N	21. cat Y N
4. balloon Y N	10. boat Y N	16. dog Y N	22. HOTEL Y N
5. coffee Y N	11. scarf Y N	17. apartment Y N	23. COW Y N
6. LION Y N	12. PEARL Y N	18. penny Y N	24. diamond Y N

Appendix E: Trail Making Test (TMT)

Test Part A:



Test Part B:



Appendix F: Patient Reported Outcomes Measurement Information System – Modified Cognitive Function

Please respond to each question or statement by marking one box per row.

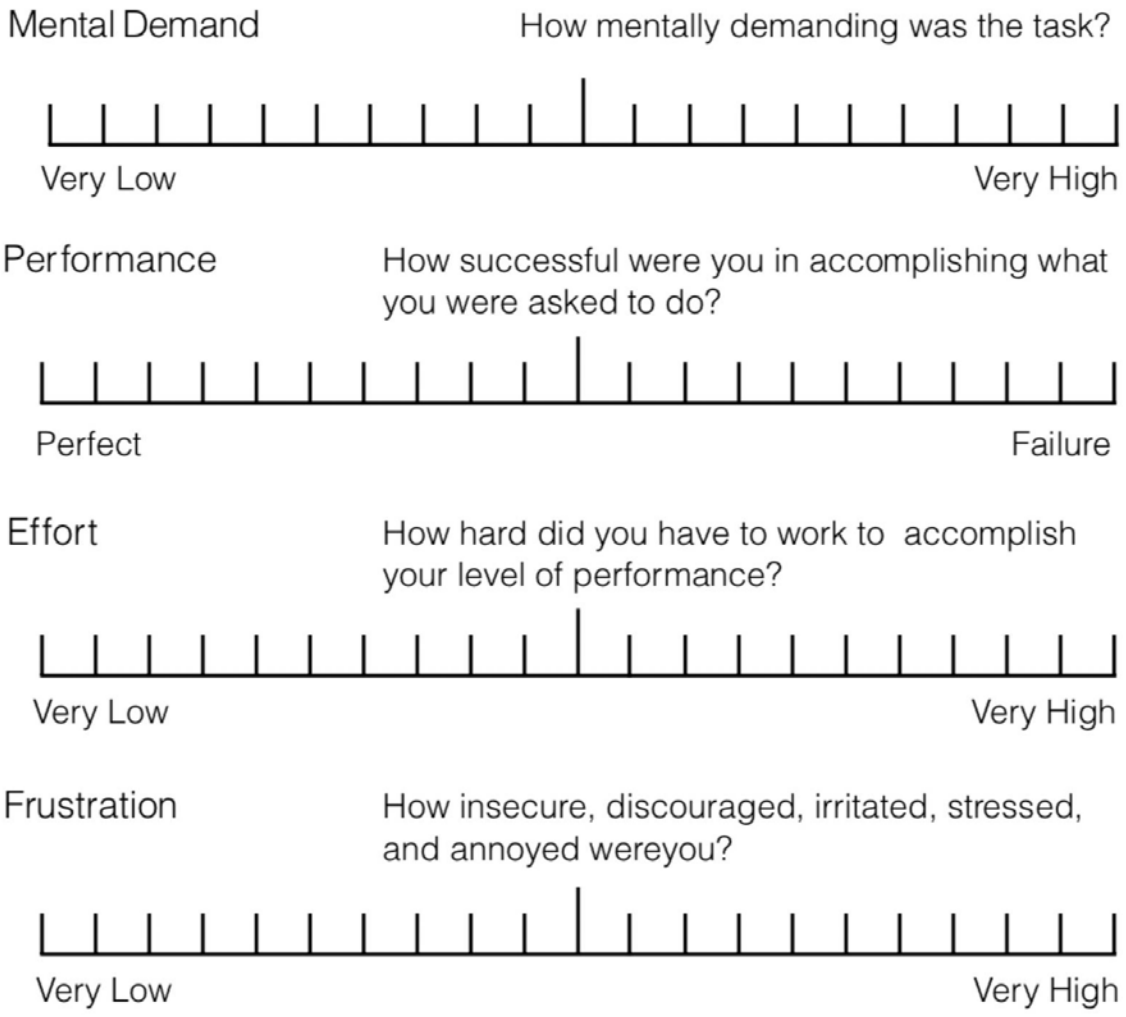
In the past 7 days...

		Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
1	My thinking has been slow.....	5	4	3	2	1
2	It has seemed like my brain was not working as well as usual.....	5	4	3	2	1
3	I have had to work harder than usual to keep track of what I was doing.....	5	4	3	2	1
4	I have had trouble shifting back and forth between different activities that require thinking	5	4	3	2	1
5	I have had trouble concentrating	5	4	3	2	1
6	I have had to work really hard to pay attention or I would make a mistake	5	4	3	2	1
7	I have had trouble forming thoughts	5	4	3	2	1
8	I have had trouble adding or subtracting numbers in my head.....	5	4	3	2	1
9	I have had trouble remembering whether I did things I was supposed to do, like taking a medicine or buying something I needed.....	5	4	3	2	1

Before my cancer diagnosis…

		Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
10	I noticed problems with my thinking.....	5	4	3	2	1
11	I had trouble remembering whether I did things I was supposed to do, like taking a medicine or buying something I needed.....	5	4	3	2	1
12	Compared to most other people my age with similar education, I was.....	☐ Not as smart		☐ As smart		☐ Smarter

Appendix G: Modified NASA Task Load Index (NASA-TLX)



Appendix H: Wechsler Adult Test of Reading (WTAR)

WORD CARD

1. again
2. address
3. cough
4. preview
5. although
6. most
7. excitement
8. know
9. plumb
10. decorate
11. fierce
12. knead
13. aisle
14. vengeance
15. prestigious
16. wreathe
17. gnat
18. amphitheater
19. lieu
20. grotesque
21. iridescent
22. ballet
23. equestrian
24. porpoise
25. aesthetic
26. conscientious
27. homily
28. malady
29. subtle
30. fecund
31. palatable
32. menagerie
33. obfuscate
34. liaison
35. exigency
36. xenophobia
37. ogre
38. scurrilous
39. ethereal
40. paradigm
41. perspicuity
42. plethora
43. lugubrious
44. treatise
45. dilettante
46. vertiginous
47. ubiquitous
48. hyperbole
49. insouciant
50. hegemony

Appendix I: PROMIS-Depression

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
1	I felt worthless.....	1	2	3	4	5
2	I felt helpless	1	2	3	4	5
3	I felt depressed	1	2	3	4	5
4	I felt hopeless	1	2	3	4	5
5	I felt like a failure.....	1	2	3	4	5
6	I felt unhappy	1	2	3	4	5
7	I felt that I had nothing to look forward to	1	2	3	4	5
8	I felt that nothing could cheer me up.....	1	2	3	4	5

Appendix J: PROMIS-Anxiety

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
1	I felt fearful	1	2	3	4	5
2	I found it hard to focus on anything other than my anxiety...	1	2	3	4	5
3	My worries overwhelmed me	1	2	3	4	5
4	I felt uneasy	1	2	3	4	5
5	I felt nervous	1	2	3	4	5
6	I felt like I needed help for my anxiety	1	2	3	4	5

Appendix K: PROMIS-Sleep Disturbance

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Very poor	Poor	Fair	Good	Very good
1	My sleep quality was.....	5	4	3	2	1

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
2	My sleep was refreshing	5	4	3	2	1
3	I had a problem with my sleep	1	2	3	4	5
4	I had difficulty falling asleep	1	2	3	4	5
5	My sleep was restless.....	1	2	3	4	5
6	I tried hard to get to sleep.....	1	2	3	4	5
7	I worried about not being able to fall asleep	1	2	3	4	5
8	I was satisfied with my sleep	5	4	3	2	1

Appendix L: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
1	I feel fatigued	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble starting things because I am tired	0	1	2	3	4
6	I have trouble finishing things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix M: Karnofsky Performance Status (KPS)

Score	Criteria
100	Normal; no complaints; no symptom of disease.
90	Able to carry on normal activity; minor symptoms of disease.
80	Normal activity with effort; some symptoms of disease.
70	Care for self. Unable to carry on normal activity or to do active work.
60	Require occasional assistance, but able to care for most of personal needs.
50	Require considerable assistance for personal care.
40	Disabled; require special care and assistance.
30	Severely disabled; require continuous nursing care.

Appendix N: Functional Assessment of Cancer Therapy-General (FACT-G)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
1	I have a lack of energy	0	1	2	3	4
2	I have nausea	0	1	2	3	4
3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4	I have pain	0	1	2	3	4
5	I am bothered by side effects of treatment	0	1	2	3	4
6	I feel ill	0	1	2	3	4
7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
8	I feel close to my friends	0	1	2	3	4
9	I get emotional support from my family	0	1	2	3	4
10	I get support from my friends	0	1	2	3	4
11	My family has accepted my illness	0	1	2	3	4
12	I am satisfied with family communication about my illness	0	1	2	3	4
13	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ *and go to the next section.*					
14	I am satisfied with my sex life	0	1	2	3	4

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
15	I feel sad	0	1	2	3	4
16	I am satisfied with how I am coping with my illness	0	1	2	3	4
17	I am losing hope in the fight against my illness	0	1	2	3	4
18	I feel nervous	0	1	2	3	4
19	I worry about dying	0	1	2	3	4
20	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
21	I am able to work (include work at home)	0	1	2	3	4
22	My work (include work at home) is fulfilling	0	1	2	3	4
23	I am able to enjoy life	0	1	2	3	4
24	I have accepted my illness	0	1	2	3	4
25	I am sleeping well	0	1	2	3	4
26	I am enjoying the things I usually do for fun	0	1	2	3	4
27	I am content with the quality of my life right now	0	1	2	3	4

Appendix O: Blessed Orientation Memory Concentration (BOMC)

Items	Maximum Error		Score		Weight
1. What year is it now?	1			× 4 =	
2. What month is it now?	1			× 3 =	
Memory phrase: Repeat phrase after me: "John Brown, 42 Market Street, Chicago."					No points
3. About what time is it, within one hour?	1			× 4 =	
4. Count backwards from 20 to one.	2			× 2 =	
5. Say the months in reverse order, starting with December.	2			× 2 =	
6. Repeat the memory phrase. [1] John [1] Brown [1] 42 [1] Market [1] Chicago	5			**TOTAL**	

Appendix P: Hormonal Status Form

Do you still have menstrual cycles (periods)?	Yes___	No___
If not, was your last menstrual cycle within the last year?	Yes___	No___
Are your menstrual cycles irregular? If yes, when did the irregularity begin?	Yes___	No___
Have you ever taken hormone replacement therapy (around the time of menopause)? If so, when did you start? If you are not still taking it, why did you stop?	Yes___	No___
Have you ever had a bad reaction to oral contraceptives/birth control pill?	Yes___	No___
Have you ever experienced significant mood changes with your menstrual cycle, pregnancy, or postpartum?	Yes___	No___

Appendix Q: Modified Brief Medication Questionnaire (BMQ)-Specific

- We would like to ask you about your personal views about memantine (the medication you took for this study).
- In the items below, "cognition" refers to your memory, concentration, and overall thinking ability.
- Please indicate the extent to which you agree or disagree with them by circling the appropriate number.
- There are no right or wrong answers. We are interested in your personal views.

		Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
1	My cognition, at present, depends on memantine	1	2	3	4	5
2	Having to take memantine worried me	1	2	3	4	5
3	My life would have been impossible without memantine	1	2	3	4	5
4	Without memantine I would have had problems with my cognition	1	2	3	4	5
5	I sometimes worried about long-term effects of memantine	1	2	3	4	5
6	Memantine is a mystery to me	1	2	3	4	5
7	My future cognition will depend on memantine	1	2	3	4	5
8	Memantine disrupted my life	1	2	3	4	5
9	I sometimes worried about becoming too dependent on memantine	1	2	3	4	5
10	Memantine protected my cognition from becoming worse	1	2	3	4	5