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Randomized Placebo-Controlled Phase 2 Pilot Study of Memantine (Namenda) for Smoking Cessation among Cancer Survivors

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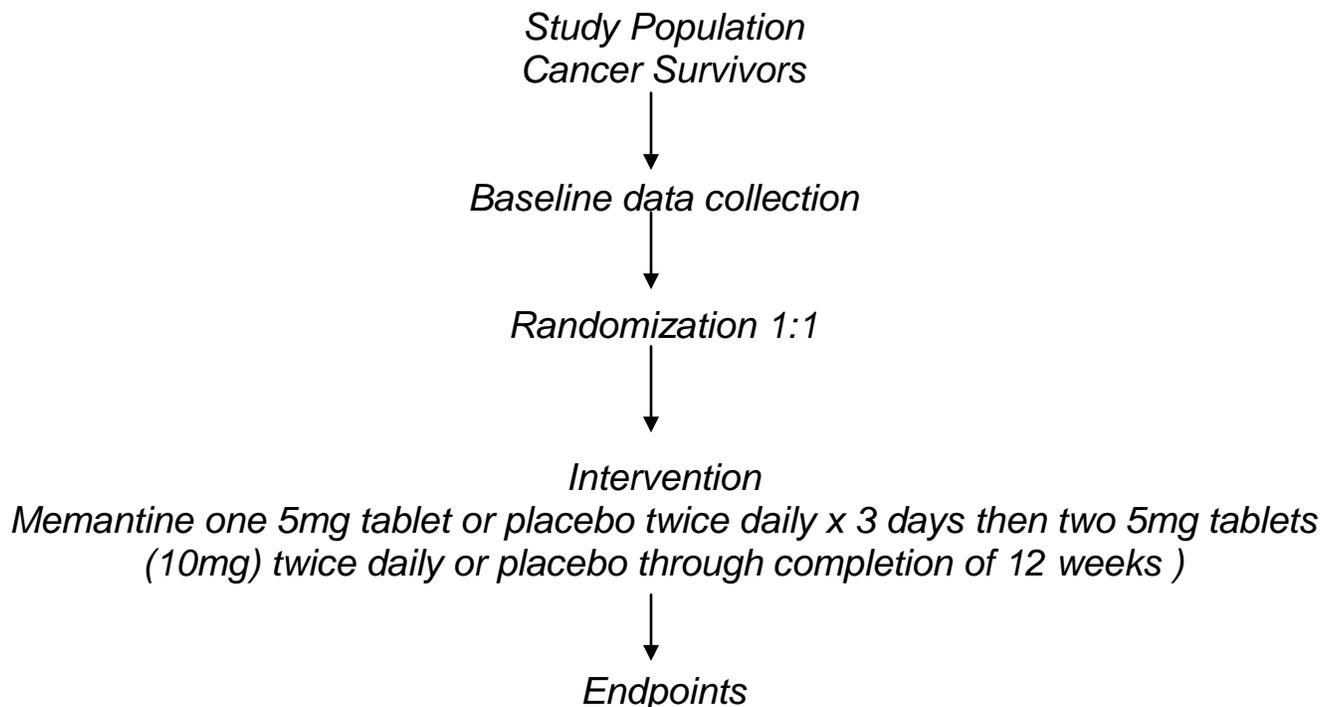
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SCHEMA

Randomized Placebo-Controlled Phase 2 Pilot Study of Memantine (Namenda) for Smoking Cessation Among Cancer Survivors



1. Estimate participation, accrual, adherence, and retention
2. Estimate the self-reported abstinence rates
3. Evaluate nicotine addiction and withdrawal symptoms
4. Evaluate quality of life
5. Evaluate side effects

Stratification: Gender

Study Sample: 130 patients (approximately 65 per arm)

Study Duration: 12 weeks

Brief Eligibility Criteria:

- Survivors of non-metastatic breast, prostate, colorectal cancers or Stage I/II non-small cell lung cancer
- Six months post definitive treatment
- Smoked 100 cigarettes over lifetime and who, at the time of the first interview, smoked 10 or more cigarettes per day on most days over the past month.
- Willingness to adhere to the study protocol and attend the required clinic visits
- Willingness to stop Nicotine Replacement Therapy (NRT) (or not start it) for duration of study

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1. OBJECTIVES

1.1. Primary protocol objectives

Since nicotine enhances the release of glutamate, and subsequently dopamine, blockade of glutamate transmission via the NMDA receptor using memantine may reduce the rewarding effects of nicotine. However, only one small study has examined this question. In this clinical trial we propose the following specific aims:

- 1.1.1 Estimate participation, accrual, adherence, and retention of cancer survivors who smoke and are randomized to receive memantine (10 mg twice daily) or a matching placebo for 12 weeks.
- 1.1.2 Estimate the self-reported abstinence rates of patients who are randomized to memantine or a matching placebo for 12 weeks. Obtain a preliminary estimate of the treatment effect (difference in abstinence rates between the two groups). The abstinence rate will be defined as self-reported one-week abstinence at 12 weeks post-randomization (have you smoked in the last week?), so this rate will be estimated in this pilot study. It will be verified using urine cotinine, a common method used in smoking cessation trials.

1.2 Secondary Endpoint(s)

The following secondary endpoints will be assessed in this study.

- 1.2.1 Nicotine addiction will be assessed using the Wisconsin Inventory of Smoking Dependent Motives.¹⁹
- 1.2.2 Nicotine withdrawal will be measured by the Wisconsin Smoking Withdrawal Scale.¹⁸
- 1.2.3 Quality of life, as measured by the SF12.
- 1.2.4 Toxicities will be assessed using the CTCAE, version 4.

2. BACKGROUND

2.1 Study Disease

2.1.1 Epidemiology of Tobacco use

Smoking is the leading cause of preventable death in the US, responsible for over 420,000 deaths annually.¹ According to the Centers for Disease Control and Prevention, in 2005, 45.1 million adults (20.9 percent) in the United States were current cigarette smokers—23.9 percent of men and 18.1 percent of women.²

2.1.2 Smoking and Cancer

Cancer is the second leading cause of death and was among the first diseases causally linked to smoking. Lung cancer is the leading cause of cancer death, and cigarette smoking causes most cases.¹ Compared to nonsmokers, men who smoke are about 23 times more likely to develop lung cancer and women who smoke are about 13 times more likely. Smoking also causes cancers of the oral cavity, pharynx, larynx, esophagus, and bladder, among other sites. For these smoking-attributable

cancers, the risk generally increases with the number of cigarettes smoked and the number of years of smoking, and generally decreases after quitting completely.¹

2.1.3 **Cancer Survivors and Smoking:**

In 2004, an estimated 1.4 million Americans will be diagnosed with cancer, joining approximately 9.8 million existing survivors.³ Using the National Health Interview Study, Belizzi and colleagues⁴ found that cancer survivors are similar to controls with respect to smoking status and alcohol use, although younger survivors (age 18-40) were at greater risk for continued smoking than controls. Despite encouraging projections of longevity after a cancer diagnosis, cancer survivors are at increased risk for recurrence, secondary cancers and late effects of treatment.³ Therefore, tertiary prevention, including smoking cessation, has received increased attention.⁴

Cancer diagnosis is an opportune time for patients to quit smoking. In a study of 352 cancer survivors recruited from four geographically diverse clinic sites,⁵ 63 (18%) participants indicated that they were cigarette smokers at the time they were diagnosed with cancer. Of these, 29 (46%) participants quit smoking after their cancer diagnosis. Although not reaching statistical significance, factors tending to increase the likelihood of smoking cessation among cancer survivors included: male gender, age > 55, African American race, higher income levels, > 1 year post-diagnosis, and >1 year since cancer treatment had stopped (odds ratio for the latter: 4.98, 95% confidence interval= 0.62-40.00).⁵

With up to 54% of cancer survivors who smoked at diagnosis still smoking,⁵ these studies suggest that smoking cessation efforts need to be increased among those who continue to smoke. Many options are available for smoking cessation in any patient⁶ e.g., intensive counseling, nicotine replacement therapy, sustained release bupropion,⁶ and varenicline.⁷ Unfortunately, none works for every smoker, and only varenicline is without drug-drug interactions.⁸ Intuitively, the availability of more therapeutic options will increase the chance that any given smoker will be successful. If that smoker is a cancer survivor, the treatment option should also be safe and without drug-drug interactions given the concomitant medications that cancer patients often are taking—some of which are quite toxic.

2.2 **Study Agent**

2.2.1 **NMDA Receptor Blockade: A Novel Tobacco Intervention Avenue**

The N-methyl-D-aspartate (NMDA) receptor is a glutamate activated ion channel with complex roles in central nervous system physiology.⁹ In particular, these receptors are involved in central excitatory pathways that are critical in higher brain functioning such as learning, memory and certain behaviors. Additionally, excessive NMDA receptor stimulation is involved with chronic pain, addiction, and neuronal cell death.^{9,10}

Nicotine use enhances glutamate (excitatory) transmission while at the same time enhancing GABA (inhibitory) transmission within brain reward pathways, the latter desensitizing rapidly. Nicotine acts on pre-synaptic nicotinic acetylcholine receptors (nAChR) of glutamate efferents located within the prefrontal cortex. These efferents project to the ventral tegmental area (VTA).¹¹ When stimulated, there is increased

glutamate release from these efferents into the VTA. Here, the increased glutamate interacts with NMDA receptors located post-synaptically on VTA dopamine neurons that project into the shell of the nucleus accumbens, increasing their firing rate.¹² This increased dopamine release into the shell of the nucleus accumbens is responsible for the rewarding and addictive properties of many drugs of abuse, including nicotine.

Simultaneously, nicotine also enhances GABAergic transmission transiently within the VTA, which is followed by a persistent depression of these inhibitory inputs due to nAChR desensitization.¹³ The nicotine enhancement of glutamatergic transmission through nAChRs desensitize less than those on GABA neurons.¹³ The net effect is a shift toward excitation of the dopamine reward system. Thus, spatial and temporal differences in nicotinic receptor activity on both excitatory and inhibitory neurons in the VTA and nucleus accumbens coordinate to reinforce nicotine self-administration.¹³ From these observations, it appears that NMDA receptors may play a role in nicotine use, and that blockade of these receptors may reduce the nicotine-induced excitatory glutamate response with the VTA.¹²

Strong indirect evidence in both animals and humans implicate the NMDA glutamergic pathway in smoking cessation.^{30,31,32} The GABA B agonist, baclofen, has an antagonistic effect on glutamate transmission via the NMDA receptor within the VTA. Franklin et. al reviewed 16 preclinical studies which examined the treatment effectiveness of baclofen on drug-seeking motivated behavior and dopamine release. In addition, memantine is effective in reducing use of other drugs of abuse. In mice treated with memantine (the glutamate/NMDA receptor antagonist) during the extinction phase of morphine were insensitive to morphine's ability to reinstate the place preference 2 days after extinction conditionings.²⁷ Among humans, memantine reduces the effects of alcohol withdrawal in moderate drinkers.²⁸ Furthermore, the GABAergic drug, gabapentin, is effective in ameliorating cocaine withdrawal.²⁹ Combined, the animal and human evidence point towards the NMDA receptor pathway as an important target for cessation of abused drugs including nicotine.

2.2.2 **Quality of Life in Smoking Cessation:**

The process of smoking cessation impacts a patient's physical and mental quality of life. Based on the SF-36, Olufade et. al developed a 5-scale instrument, the Smoking Cessation Quality of Life (SCQoL) Questionnaire, that focused on social interactions, self-control, sleep, cognitive functioning and anxiety.³³ They found this instrument to be reliable and valid in measuring physical and mental functioning during smoking cessation. In their next study³⁴, the SCQoL indicated that recidivists who return to smoking during 6 weeks of follow up were more likely to report a greater number of (and more severe) smoking cessation adverse quality of life symptoms than those who remained completely abstinent ("successful quitters"). If memantine helps with smoking cessation, it theoretically should ameliorate adverse physical and mental functioning symptoms, perhaps by blocking excessive excitatory pathways via the NMDA receptor. In alcohol withdrawal, for example, it has been shown that the NMDA receptor system is highly involved in adverse symptomatology.³⁵

Another quality of life issue of tobacco cessation voiced by non-cancer patients is weight gain post-cessation. Although it is unclear if this same concern exists among cancer survivors attempting to quit smoking, there are data to suggest that memantine might moderate weight gain. Studies among both humans and baboons have shown that

memantine normalizes eating behavior likely by enhancing satiation.^{23,24,25,26} Thus, memantine might help avoid weight gain among patients who quit smoking using this drug.

2.2.3 **Literature Review**

One currently marketed drug, memantine (Namenda), has activity against the excitatory effects of glutamate. Memantine is a low affinity NMDA receptor antagonist with weaker antagonism at nicotinic acetylcholine receptors.¹⁰ It has been approved for use in Alzheimer's disease, likely exerting its action by ameliorating glutamatergic excitotoxicity. There is also evidence that memantine may have a positive role in treating nicotine abuse.¹⁴ A pilot study among 40 smokers¹⁵ revealed that memantine helped with certain aspects of nicotine's effects. Memantine showed trends toward decreased smoking scores, though not statistically significant due to a small sample size. Indeed, memantine decreased olfactory hedonic ("likeability") estimates of R-(+)-nicotine enantiomer by 17.8% compared to an *increase* in olfactory hedonic estimates of 6.2% amongst the placebo patients. Results for the S-(-)-nicotine olfactory hedonic scores also favored memantine versus placebo (reduction of 6.7% vs. 1.2%, respectively).¹⁵ In other words, nicotine became less pleasant in the memantine group compared to the placebo group, the latter of which either increased or barely decreased the likeability of a nicotine olfactory stimulus. Weaknesses of this study were the small sample size (20 participants per group of memantine and placebo), inadequate power to find differences, and treatment duration of only 2 weeks, which might not have allowed maximum attainment of receptor responsiveness. Memantine, however, was not associated with a significant frequency of adverse events in this¹⁵ and other trials.^{16,17} These results argue for a longer duration trial and the need for additional data. The dose of memantine used in this pilot study was 10 mg bid, consistent with the dose recommended by the manufacturer for Alzheimer's Disease (Namenda® Prescribing Information. Forest Pharmaceuticals, Inc. St Louis, Mo. Accessed at: <http://www.namenda.com/sections/30/starting-namenda.shtml#fn1>).

2.2.4 **Clinical Experience:**

Dr. Spangler was one of the initial investigators to publish on memantine's proposed usefulness in smoking cessation, noting, as mentioned above, blockade of glutamate released from afferents from the prefrontal cortex to the VTA may ultimately lead to diminished release of dopamine in the nucleus accumbans.¹⁸ Additionally, in his clinical practice, Dr. J.G. Spangler has used memantine with some success in tobacco cessation. Three out of seven patients using memantine noted decreased nicotine craving and were able to remain abstinent for at least four weeks. An additional patient was able to cut down from over one pack of cigarettes daily to one cigarette daily, with marked reduction in craving. This medication was well tolerated. To evaluate the effectiveness of memantine in tobacco cessation, a clinical trial is warranted. Focusing the trial among cancer survivors via CCOPs is an efficient way to recruit patients, and in addition addresses this often neglected population in smoking cessation research.⁵

2.2.5 **Dose and Schedule for Intervention together with Justification**

Participants will be randomized to either the active intervention which will receive 10 mg of memantine per day (one 5 mg tablet twice daily) or placebo days 1-3, then 20 mg per day

(two 5 mg tablets (10 mg) twice daily) or placebo by mouth through completion of 12 weeks as carried out by Thuerauf et al.¹⁵ This schedule, though different from the titration schedule used in Alzheimer's Disease studies (e.g., titration to 10 mg twice daily over 4 weeks), was well-tolerated in that study,¹⁵ which was also a smoking cessation intervention among adults. Patients in the proposed study will differ from those in Thuerauf et al.'s study by the fact that they are cancer survivors. This should not affect the tolerability of these patients to memantine, a drug already shown to be well-tolerated.^{15, 16} As mentioned, the titration schedule and dose of memantine used in this pilot study is consistent with the dose recommended by the manufacturer for Alzheimer's Disease (Namenda Prescribing Information, Forest Pharmaceuticals, Inc., St. Louis, MO, accessed at: <http://www.namenda.com/sections/30/starting-namenda.shtml#fn1>) and with the prior small, short term RCT using memantine in smoking cessation.¹⁵

2.3 RATIONALE

Since nicotine enhances the release of glutamate, and subsequently dopamine, blockade of glutamate transmission via the NMDA receptor using memantine may reduce the rewarding effects of nicotine. However, only one small study has examined this question.

3.0 SUMMARY OF STUDY PLAN

This is a randomized, placebo controlled, pilot study assessing the feasibility of a smoking cessation intervention in cancer survivors. Patients will be stratified by gender and assigned with equal probability to memantine or a matched placebo using random permuted block randomization. The objectives for this trial are: 1) to estimate accrual, retention, adherence, and participation rates, 2) to obtain a preliminary estimate of the treatment effect (difference in abstinence rates in the two groups), 3) to estimate the variability of and treatment effect on nicotine addiction, nicotine withdrawal symptoms, and quality of life, and 4) to estimate the rates of toxicity and adverse events associated with memantine.

There will be 130 participants with 65 participants per arm. A brief description of the study population includes survivors of breast, prostate, colorectal cancers or Stage I/II non-small cell lung cancer. (These survivors were chosen because of improved longevity rates for these cancers³ enhancing the long term impact of smoking cessation; and probable association of these cancers with cigarette smoking.¹)

Planned intervention: Participants will be randomized to either the active intervention which will receive 10 mg of memantine per day (one 5 mg tablet twice daily) days 1-3, then 20 mg per day (two 5 mg, tablets (10 mg) twice daily) or placebo by mouth through completion of 12 weeks. Participants randomized to inactive intervention will receive a placebo.

Time points for performing study assessments: questionnaires will be completed at baseline and every two weeks for a total of 12 weeks. A urine cotinine test will also be collected at weeks 4, 8 and 12.

Duration of study intervention 12 weeks.

4.0 PARTICIPANT SELECTION

4.1 Inclusion Criteria

- 4.1.1 Survivors of non-metastatic breast, prostate, colorectal cancers or Stage I/II non-small cell lung cancer.
- 4.1.2 Age \geq 18 years.
- 4.1.3 ECOG performance status 0 - 1 (Karnofsky \geq 70%; see Appendix 3)
- 4.1.4 Ability to understand and the willingness to sign a written informed consent document.
- 4.1.5 Six months post definitive treatment (except for ongoing hormonal or targeted therapies)
- 4.1.6 Smoked 100 tobacco cigarettes over lifetime at time of first interview, have smoked 10 or more cigarettes per day on most days over the past month.
- 4.1.7 Agrees to adhere to the study protocol and attend the required clinic visits.
- 4.1.8 Patients currently must not be taking Nicotine Replacement Therapy (NRT) and agree to not start Nicotine Replacement Therapy (NRT) for the duration of the study.
- 4.1.9 Patients currently taking antidepressant or anti-anxiety medications must have been on a stable dose for 4 weeks prior to registration.
- 4.1.10 Negative serum pregnancy test within 10 days prior to registration in women with child-bearing potential. The effects of memantine on the developing human fetus at the recommended therapeutic dose are unknown. For this reason women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.
- 4.1.11 It is unknown whether memantine is excreted in breast milk, for this reason women who are currently breast-feeding are not eligible for this study.

4.2 Exclusion Criteria

- 4.2.1 Use of chewing tobacco, pipe tobacco, snuff or any other non cigarette tobacco product is not allowed.
- 4.2.2 Patients with clinically significant uncontrolled medical conditions (e.g., unstable angina, myocardial infarction, TIA or CVA) within past 3 months
- 4.2.3 History of renal and/or hepatic dysfunction or disease
- 4.2.4 Current uncontrolled hypertension \geq 160/90

- 4.2.5 Excessive alcohol abuse defined as more than 5 drinks per day for men and 4 drinks per day for women.
- 4.2.6 Current use of illegal drugs or use of prescription medications for non-medical reasons.
- 4.2.7 Patients currently receiving the following medications are not eligible: anticonvulsant agents (e.g., phenytoin, carbamazepine, gabapentin, etc.); antiparkinsonian agents (e.g., Levo Dopa, ropinirole); neuroleptic agents (e.g., risperidone, quetiapine), carbonic anhydrase inhibitors (e.g., Diamox® and Sequels®) Memantine should not be combined with other NMDA antagonists (amantadine, ketamine, and dextromethorphan).
- 4.2.8 Major medical or psychiatric illness which, in the opinion of the investigator, would prevent completion of treatment or would interfere with follow-up.
- 4.2.9 Participants may not be receiving any other investigational agents.
- 4.2.10 History of allergic reactions attributed to memantine.
- 4.2.11 Participants using the following medications while on this study: Antiparkinson medications (Ex. Amantadine (Symmetrel)), anticonvulsant agents, surgical anesthesia drugs (Ex. Ketamine), carbon anhydrase inhibitors (Ex. Acetazolamide (Diamox)) or cough suppressants (Dextromethorphan).

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

Race/Ethnicity

| Gender | White, not of Hispanic Origin | Black, not of Hispanic Origin | Hispanic | Asian or Pacific Islander | Unknown | Total |
|---------------|--------------------------------------|--------------------------------------|-----------------|----------------------------------|----------------|--------------|
| Male | 64 | 12 | 2 | 0 | 0 | 78 |
| Female | 43 | 8 | 1 | 0 | 0 | 52 |
| Total | 107 | 20 | 3 | 0 | 0 | 130 |

4.4 Recruitment and Retention Plan

The targeted cancer survivorship groups are well represented among the CCCWFU Research Base membership. Recruiting to this protocol should be quite feasible, given the level of interest in smoking cessation among cancer survivors. A survey of Research Base sites regarding the proposed protocol was conducted. Twelve of 25 CCOPs responded. Estimated accrual by those 12 CCOPs was 454 patients per year. Extending these accrual estimates to our entire Research Base (25 CCOPs, Wake Forest, and our 2 non-CCOP sites), even if only one in four potentially eligible patients is enrolled on study, we should be able to complete accrual in 18 months.

A participant sample recruitment poster and a recruitment letter are included in the appendices.

Minority recruitment strategies for discussion/consideration:

- Minority Base CCOPs will be identified for recruitment.
- Site specific recruitment information to minority community leaders is encouraged according to site specific institutional policy.
- Sites may perform cultural assessments for local community regions according to the site institutional policy.

The research PI or designee at each site will determine participant eligibility according to site specific regulations, and may include the clinic physician..

Accrual is expected to be 7-8 patients per month. Targeted accrual should be met in approximately 18 months. A maximum of 130 patients will be enrolled on this trial. Patients will be followed for 12 weeks. After the 12 week visit, the patient is no longer followed and data is no longer collected from the patient.

5. AGENT ADMINISTRATION

5.1 Dose Regimen and Dose Groups

Participants randomized to the active intervention will receive 10 mg of memantine per day (one 5 mg tablet twice daily) days 1-3, then 20 mg per day (two 5 mg tablets (10 mg) twice daily until study completion after 81 days) Participants randomized to inactive intervention will receive a placebo.

5.2 Memantine Administration

- Take dose once in the morning and once in the evening by mouth.
- May be taken with or without meals. Take at the same time every day.

5.3 Contraindications

Contraindications: allergy to memantine, patient use of carbonic anhydrase inhibitors or anticonvulsant agents, antiparkinsonian agents and pregnancy.

5.4 Concomitant Medications

Combined use of memantine with other NDMA antagonists (amantadine, ketamine or dextromethorphan (found in cough syrups)) should be avoided.

5.5 Dose Modification

There are no dose modifications, such as dose reductions, allowed. If patients do not tolerate the study agent, they will be taken "off treatment" but remain on study to continue providing data. Missed doses do not need to be made up however they should be recorded in the medication diary.

5.6 Adherence/Compliance

5.6.1 Adherence will be calculated 1) as the number of tablets taken divided by the ideal number of tablets that could have been taken while on study; and 2) as the number of tablets taken divided by the number of tablets that could be taken if the participant completed the study. Estimation of adherence is one of the objectives of this pilot study. All patients, even those who do not complete therapy or are not fully adherent, will be included in the analyses used to estimate the treatment effect. We do not plan on using imputation for the primary analysis, although imputation may be use in sensitivity analyses. The longitudinal models described below assume missing data are missing at random (missingness could depend on covariates or previous responses but not on the missing response). We will assess the effects of patient characteristics on missingness and include any that are associated with missingness in the longitudinal models.

5.6.2 Methods used to monitor each participant's compliance include: diaries, tablet counts, urine cotinine.

6. PHARMACEUTICAL INFORMATION

6.1 Memantine and Placebo

Memantine is manufactured by Forest Pharmaceuticals, Inc. from whom the drug and placebo will be purchased. Both will be provided to participants at no cost.

6.2 Reported Adverse Events and Potential Risks

Most Common/Likely side effects (expected to occur in greater than 10% of patients):

- None

Less Likely side effects (expected to occur in less than 10% of patients):

- Dizziness
- Confusion
- Headache
- Constipation
- Coughing
- Extreme tiredness
- Sleepiness
- Vomiting
- Backache
- Shortness of breath
- Hallucinations
- Diarrhea
- Elevated blood pressure

Rare but Serious (expected to occur in less than 2% of patients):

- Stroke
- Seizures
- Severe skin reaction
- Blood clots
- Liver failure
- Renal failure

6.3 Availability

Memantine is provided by the study at no cost to patients.

6.4 Agent Ordering and Distribution

Distribution of study drug and placebo will be performed by Biologics, Inc. Upon notification of a new patient registration, Biologics places an outbound call to the site contact confirming their shipment is being processed, Biologics will request the following patient specific information (patient name/initials, prescriber name, site shipping address and phone number) and provide the courier, date and time of anticipated delivery.

- Biologics, Inc. will send entire supply of study drug for each patient enrolled directly to the site for dispensing (WFU exempt). Each patient specific shipment will include three, four week bottles of study drug with patient specific labels.

Biologics ships study drug “same day” for orders received before 2:00 p.m. EST Monday through Thursday. Orders received after 2:00 p.m. Monday through Thursday will be processed the next business morning. All shipments are sent via Federal Express Second Day Delivery. Biologics distribution team monitors packages throughout duration of transit via Federal Express website.

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

Institutions should document drug accountability using the NCI DARF

6.6 Packaging and Labels

Memantine (Namenda) 5 mg Tablets
Placebo Tablets

The agents will be administered orally by the patient as follows:

10 mg of memantine per day (one 5 mg tablet twice daily) days 1-3, then 20 mg per day (two 5 mg tablets (10 mg) twice daily until study completion after 81 days)

Days 1-3: Memantine 10 mg per day (one 5 mg tablet twice daily) (one tablet in the morning and one tablet in the evening.)

Day 4- 84: Memantine 20 mg per day (two 5 mg tablets (10 mg) twice daily until study completion after 81 days) (two tablets in the morning and two tablets in the evening.)

Each patient will be dispensed three bottles of study drug. Each bottle will be labeled with patient specific information that includes the following:

- Protocol #/ brief name
- Patient's name/initials
- Administration instructions/signatures
- Dr.'s name
- Dispense date
- Expiration date
- Storage instructions

Each bottle will also include an auxiliary label on the lid of the bottle with the following information:

- Bottle 1 – Weeks 1-4
- Bottle 2 – Weeks 5-8
- Bottle 3 – Weeks 9-12

Each bottle will have a four week supply of medication. The quantities of each bottle will be as follows, to accommodate the change in dosing at day 4:

- Bottle 1 will contain 106 tablets
- Bottle 2 will contain 112 tablets
- Bottle 3 will contain 112 tablets

6.7 Storage

Memantine/Placebo should be stored at room temperature.

6.8 Registration/Randomization

6.8.1 Registration Process

IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax: (336)716-6275

Fill out Appendix 2, "Eligibility Checklist / Registration Form". Use this to complete the on-line registration.

Online Registration

Log on to the CCCWFU Research Base registration web site at < <https://ccrbis.phs.wfubmc.edu>>. Enter your user name and password (which may be obtained by contacting June Fletcher-Steede at jsteede@wakehealth.edu.) *In the 'Patient Registration and Protocol Information' table, click the 'Register Patient/Patient Info', with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the drop down boxes.* Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. Print this confirmation sheet for your records. See Section 11.1 data management schedule for any forms that should be faxed to 336-713-6476 or mailed to Data Management:

Research Base Data Management Center
Department of Radiation Oncology
1st Floor Cancer Center
WFBMC
Medical Center Boulevard
Winston-Salem, NC 27157

These forms should be retained in the patient's study file and will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-3172 or 713-6507.

6.8.2 Randomization Process

Permuted variable block randomization with strata defined by gender will be used to assign patients to a treatment (see Section 13.3).

6.9 Unblinding Methods

In the event a patient on this study develops a toxicity (adverse event or severe adverse event) for which the patient's physician or other health care professional feels that it is in the patient's best interest to know what drug they are taking (active study drug(s) or placebo), the following procedure should be followed:

- Step 1: The patient's physician or a designated health care professional should call the Wake Forest University Baptist Medical Center Physician Access Line (336-716-7654) and ask that Dr. Ed Shaw, Principal Investigator of the CCCWFU CCOP Research Base, be contacted immediately either in his office, by pager, or at home. In the event Dr. Shaw cannot be reached, the PAL operator should contact Dr. Glenn Lesser, Director, Symptom Treatment Protocols in his office, by pager, or at home. If neither Dr. Shaw nor Dr. Lesser can be reached, the PAL operator should contact Gina Enevold, GNP, Research Base Administrator, either in her office or at home.
- Step 2: Once contact has been made; the patient's physician or health care professional should explain the reason for the request to unblind the treatment arm that the patient is

on. If the Research Base representative feels that the toxicity (AE/SAE) is possibly, probably or definitely related to the study drug, then the next step will be followed.

- Step 3: The responsible Research Base representative will call the pharmacist @ Biologics, Inc. (phone: 1-800-850-4306). There is an “on-call” service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The Biologics pharmacist may contact the patients’ physician and/or health care professional directly with the unblinding information. Written documentations of the unblinding process will be sent to the Research Base Principal Investigator by Biologics, Inc.
- Step 4: In the event that the patient’s treatment is unblinded, that patient will be taken off study with no further study follow-up. Appropriate procedures for grading toxicities, assigning causality, and reporting severe adverse events (if applicable), should be followed for each protocol for all Phase II and Phase III Clinical Trials. The event will be reviewed by the CCCWFU Clinical Research Oversight Committee and reviewed by the CCOP Research Base Data Safety and Monitoring Board.

Record the details of the adverse event and/or unblinding in the site source documentation and complete appropriate AE forms.

Unblinding Study Participants at Study Completion

Study Participants may be unblinded at the conclusion of the study if all patient specific data for the requesting site are completed and submitted to the DMC.

Site members can obtain unblinding information by sending an email request to the CCCWFU CCOP Administrator or Data Management Supervisor with a list of PID #s.

After confirming with the DMC that patient specific data for all patients at the requesting site have been received, completed and entered into the RB database, Biologics, Inc will be notified. An email from Biologics, Inc containing the unblinding information will be sent directly to the requesting site.

6.9.1 Agent Destruction/Disposal

Unused drug/placebo should be destroyed on site following site institutional policies and procedures. Destruction of study agent should be documented using the NCI DARF (see Section 6.5)

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Medical History Screen and Exam is required within 6 months of registration that includes a general medical history and exam to ensure that they have no health conditions or medications that would preclude their ability to participate in this study. Demographics including age, race/ethnicity, education, occupation, marital status, and health insurance status will be collected.

Behavioral Risk Factor Surveillance Survey (BRFSS) is a Smoking Status Questionnaire and includes standardized questions that will be used at baseline to assess the patients' smoking history including, age at smoking initiation, number of years smoked, frequency of cigarettes per day & month, and number of quit attempts. Also, we will collect information on other smoking cessation classes or therapies that the participants may have used in the past to quit smoking.

Self-reported Tobacco Abstinence A single questionnaire item (i.e., Have you smoked a cigarette, even a puff, over the past 7 days?) will be used at 2, 4, 6, 8, 10 and 12 weeks to assess tobacco use.

Urine Cotinine Test (NicAlert) Self-contained, ready to use, point of contact drug testing device that detects the presence of cotinine, the principal metabolite of nicotine in human urine samples. This kit contains a highly sensitive chromo graphic lateral flow strip testing device along with a special collection device for human urine samples, Using the preferred lateral flow immunoassay technology the test is extremely sensitive to cotinine and will detect 6 ranges of cotinine concentrations from 0 ng/ml through 2000+ ng/ml. This method of test screening requires no special training to complete and semi-quantitative results are visibly obtained within approximately 15 minutes. Urine Cotinine will be collected and results recorded on the flow sheet at 4, 8, and 12 weeks. Follow the instructions that are included in the kit. Kits can be requested after IRB approval on the Research Base website: <https://www.wakehealth.edu/CCOP-Research-Base/99311-NicAlert-Kit-Request-Form.htm>

Wisconsin Inventory of Smoking Dependent Motives.²⁰ This instrument will be used to assess nicotine addiction. It is a multidimensional measure of nicotine dependence based on theoretically-grounded motives for drug use. Validity measures show that it significantly correlates with dependence criteria such as smoking heaviness, dependence and relapse as spelled out in the DSM-IV, and will assess changes in dependence and correlates of relapse among participants at baseline and at weeks 2, 4, 6, 8, 10 and 12 during the study.

Wisconsin Smoking Withdrawal Scale.¹⁸ This scale will be used at baseline and weeks 2,4,6,8,10 and 12 to assess symptoms related to nicotine withdrawal among the study participants. It contains 7 reliable subscales which measure the major symptoms of the nicotine withdrawal syndrome, and will assess severity of nicotine withdrawal among participants over the 12 weeks of the study.

SF-12 The SF-12 is a brief 12-item measure of quality of life. This form is a reduced form of the SF-36, and contains both a physical health and a mental health component. This measure will be used to assess the impact of treatment on patients' quality of life over the course of the 12 week treatment period, specifically at baseline, 4, 8, and 12 weeks.

Fagerstrom Nicotine Tolerance Scale: a widely used, written test of nicotine dependence- the Fagerstrom Tolerance Questionnaire (FTQ). The FTQ correlates with other proposed measures of nicotine dependence (carbon monoxide, nicotine, and cotinine levels). In placebo-controlled trials, FTQ scores were also related to success by treatment.³⁶

7.2 Baseline Testing/Pre-study Evaluation

- Medical history; demographics and exam within the past 6 months.
- Pregnancy test (within 10 days of registration) if applicable
- Behavioral Risk Factor Surveillance System (BRFSS)

- Fagerstom Nicotine Tolerance Scale
- Wisconsin Inventory of Smoking Dependent Motives Instrument
- Wisconsin Smoking Withdrawal Scale
- SF12

7.3 Evaluations during Study Intervention

Assessments to be completed at baseline and weeks 2, 4, 6, 8, 10 and 12:

- Self-Reported Tobacco Abstinence
- Urine Cotinine Test (Baseline, and weeks 4, 8, 12 only)
- Fagerstom Nicotine Tolerance Scale
- Wisconsin Inventory of Smoking Dependent Motives Instrument
- Wisconsin Smoking Withdrawal Scale
- SF12 (Baseline, and weeks 4, 8, 12 only)

7.4 Evaluations at Completion of Study Intervention

After the 12 week visit, the patient is no longer followed and data is no longer collected from the patient.

7.5 Study Parameters Table

Baseline data must be performed within 6 months of registration.

| | Baseline | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 | Week 12 |
|--|----------|--------|--------|--------|--------|---------|---------|
| Medical Exam, H & P (A) | X | | | | | | |
| Informed consent | X | | | | | | |
| Serum pregnancy test (B) | X | | | | | | |
| Behavioral Risk Factor Surveillance System BRFSS | X | | | | | | |
| Self-Reported Tobacco Abstinence Question | | X | X | X | X | X | X |
| Urine Cotinine Test | | | X | | X | | X |
| Fagerstrom Nicotine Tolerance Scale | X | X | X | X | X | X | X |
| Wisconsin Inventory of Smoking Dependent Motives | X | X | X | X | X | X | X |
| Wisconsin Smoking Withdrawal Scale | X | X | X | X | X | X | X |
| SF12 | X | | X | | X | | X |
| Medication Diary | | | X | | X | | X |
| Flow Sheet/TAS | X | X | X | X | X | X | X |

(A) The Physical Exam may be completed by a physician, PA or NP

(B) Negative serum pregnancy test is required in women of child-bearing potential within 10 days of registration.

7.6 Off Treatment Criteria

Participants may stop taking memantine for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, medical contraindication.

Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

7.7 Off Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, or death.

8. Protocol Specific Training Requirements - NA

9. SPECIMEN MANAGEMENT

9.1 Urine Cotinine Test

The test kit provides an easy office/clinic procedure and gives a semi-quantitative results using urine in approximately 15 minutes.

Extremely sensitive to cotinine, the principle metabolite of nicotine, the test will detect 6 ranges of cotinine concentrations from 0 ng/ml through 2000+ ng/ml. Highly sensitive chromo graphic lateral flow strip type testing device along with a special collection device for human urine samples, the nicotine test is a self-contained, ready to use, point of contact drug testing device that detects the presence of cotinine, the principal metabolite of nicotine in human urine samples. Using the preferred lateral flow immunoassay technology for this method of test screening, the test requires no special training to complete and semi-quantitative results are visibly obtained within minutes.

9.2 Obtaining the Urine Cotinine Test Kits

The test kits will be provided to sites at no cost by the CCCWFU CCOP Research Base. When the RB PIO receives the site's IRB approval letter to open the study, the site can request 5 kits to have on hand for the initial participant accruals. Additional kits will be sent upon site request. Kits can be requested on the Research Base website:
<https://www.wakehealth.edu/CCOP-Research-Base/99311-NicAlert-Kit-Request-Form.htm>

9.3 Urine Cotinine Test Procedure and Results

Follow instructions provided in the Urine Cotinine kit. Document the results on the flowsheet.

Each test kit contains the following items: 1 individually packaged single use test strip; 1 urine collection cup; 1 test procedure card providing step-by-step instructions for completing the test and determining the test results and detailed instruction/question and answer sheet.

10 REPORTABLE ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

- A list of adverse events/serious adverse events that have occurred or might occur that are related to this study intervention can be found in Section 6.2.
- Adverse Event/Serious Adverse Event reporting begins after the informed consent is signed
- Serious Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

10.1 Protocol Specific Reporting for Adverse Events (AEs)

- DEFINITION: An adverse event (AE) is any untoward medical occurrence in a study participant.

- Grades 1, 2, and 3 expected (solicited) and unexpected (unsolicited) AEs that meet the above definition for an AE and are ONLY definitely related, possibly related or probably related to this study intervention should be reported to the RB DMC using the Toxicity Assessment Sheet.

10.2 Protocol Specific Reporting for Serious Adverse Events (SAEs)

DEFINITION: ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997 define serious adverse events as those events which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.
- Grades 3, 4, and 5 expected (solicited) and unexpected (unsolicited) SAEs that meet the above definition for SAEs and/or regardless of attribution (i.e. regardless of whether they are related to this study intervention or not) should be reported to the RB DMC using the FDA Form 3500 (MedWatch).
- Site staff and/or Principal Investigators will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and/or fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to the study intervention.

Otherwise, the MedWatch should be sent to the RB DMC by fax or email within 10 working days of discovering the details of the SAE.

Data Elements to include on the MedWatch are:

- SAE reported date
- CTCAE Term (v4.03)
- Event onset date and event ended date
- Severity grade (use table provided in Section 10.3 below)
- Attribution to study intervention (relatedness)
- Action taken with the study participant and intervention
- Outcome of the event
- Comments

10.3 Guidelines to determine grade and severity of AEs and/or SAEs

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

| Grade | Severity | Description |
|--------------|------------------|--|
| 1 | Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*. |
| 3 | Severe | Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| 4 | Life threatening | Life-threatening consequences; urgent intervention indicated. |
| 5 | Fatal | Death related to AE. |

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Research Base Grant PI, Safety and Toxicity Review Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

The RB DMC is responsible for communicating AEs/SAEs to the FDA, the drug sponsor, WFU IRB, the WFU Safety and Toxicity Review Committee (STRC) and/or other regulatory agencies as appropriate.

Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.

10.4 Follow-up of SAEs

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the MedWatch form in the appropriate format. Follow-up information should be sent to the RB Data Management Center as soon as available.

SAEs (Grade 4 and/or Grade 5) for this protocol should be followed for those related to the study intervention. Documentation should include:

- PID
- Date of SAE
- Description of the event
- Relationship of the SAE to the study intervention
- Severity
- Intervention/Resolution

11. STUDY MONITORING

11.1 Data Management Schedule

The Eligibility checklist/Registration Form should be completed on-line prior to placing the patient on study Data forms will be submitted to the CCCWFU CCOP Research Base. See address above or faxed to (336) 713-6476 according to the Data Submission Checklist. (Appendix 1)

11.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

11.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

11.4 Data and Safety Monitoring Board

The Data Safety Monitoring Board meets every 6 months to review all phase II and phase III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the statistician. Areas of review may include the following: Date study Opened; Study Objectives; Patient Accrual; Patient Status and Retention; Study Status; Last Contact Status; Patient Compliance; Number of Biopsies/Labs as needed; Patient Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to Drug, Arm assigned; Summary of Secondary Measures.

11.5 Record retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, and NCI/DCP requirements unless the standard at the site is more stringent.

Record retention should be 5 years after the study is discontinued for studies without an IND (21 CFR 312.62).

11.6 CDUS Reporting

The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS).

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a randomized, placebo controlled, pilot study assessing the feasibility of a smoking cessation intervention in cancer survivors. Patients will be assigned with equal probability to memantine or a matched placebo using random permuted block randomization. The objectives for this trial are: 1) to estimate accrual, retention, adherence, and participation rates, 2) to obtain a preliminary estimate of the treatment effect (difference in abstinence rates in the two groups), 3) to estimate the variability of and treatment effect on nicotine addiction, nicotine withdrawal symptoms, and quality of life, and 4) to estimate the rates of toxicity and adverse events associated with memantine. Estimates of treatment efficacy will be obtained using the 'intent to treat' approach. That is, all randomized participants will be used in the analyses, regardless of whether the participants were treated according to protocol.

12.1.1 Intervention Plan and Study Design

The purpose of this randomized, pilot trial with a placebo control group is to assess the feasibility of conducting a large intervention study to test the effect of memantine on smoking cessation over 12 weeks of treatment in cancer survivors who smoke 10 or more cigarettes a day. We have not previously conducted a smoking cessation study in our Research Base, and this study will provide valuable information on our ability to recruit and retain patients to such a study, as well as data on patient adherence and preliminary estimates of treatment effect, all of which are needed to design a large phase 3 intervention study. Patients will be identified and screened by staff at participating CCCWFU Research Base member institutions. Patients meeting the eligibility criteria and signing informed consent will complete the baseline study forms and will be randomized to receive Memantine 5 mg or placebo twice daily for 3 days then 10 mg twice daily or a matching placebo for 12 weeks. All participants will also be given tailored behavioral strategies at baseline to assist them in attempting to quit/reduce cigarette smoking. Participants will also be required to return to clinic at 4, 8, and 12 weeks post-registration/randomization for interim assessments. These clinic visits will also be used as a means of encouraging smoking cessation and study compliance. Participants will not be allowed to use Nicotine Replacement Therapy (NRT) during the study

12.1.2 Definitions for Primary and Secondary Endpoints

The following endpoints will be assessed in this study.

- 1) Accrual – number of patients accrued divided by the number of months the study was open.
- 2) Retention – proportion of participants who complete the 12 week treatment period.
- 3) Adherence – a) as the proportion of tablets taken while on treatment; and b) as the proportion of the total number of tablets that could be taken if the participant completed the study. We will calculate and report the mean adherence across all individuals as well as the proportion of patients who were 75% adherent (using both definitions of adherence).

- 4) Patient participation – number of patients seen at each site who are randomized of those who met the eligibility criteria. For those who refuse to participate, reasons will be noted to assist in implementing strategies to enhance participation.
- 5) Abstinence rate – The primary endpoint in the subsequent phase 3 trial will likely be self-reported one-week abstinence at 12 weeks post-randomization (have you smoked in the last week?), so this rate will be estimated in this pilot study. It will be verified using urine cotinine, a common method used in smoking cessation trials. Both the self-reported and objective (urine cotinine verified) rates will be analyzed.
- 6) Nicotine addiction will be assessed using the Wisconsin Inventory of Smoking Dependent Motives.¹⁹
- 7) Nicotine withdrawal will be measured by the Wisconsin Smoking Withdrawal Scale.¹⁸
- 8) Quality of life, as measured by the SF12.
- 9) Toxicities will be assessed using the CTCAE, version 4.03.

12.2 Sample Size/Accrual Rate

While this is a pilot study and we will not be testing the effect of the intervention, we do want to be able to estimate the treatment effect with a fair degree of precision. Thus, the sample size for this trial will be determined to provide a reasonably tight estimate of the treatment effect. Using 1:1 randomization, we will need a total of 98 patients to estimate the difference in quit rates to within $\pm 20\%$ with 95% confidence (assuming conservatively quit rates of 0.5 in both groups). (The actual confidence interval will likely be smaller as the quit rates will probably be in the .2 to .4 range.) Even though retention will be stressed throughout the trial, and patients who refuse treatment will be encouraged to remain in the study to provide outcome data, some patients will drop out of the study. Assuming that approximately 25% of the patients will drop out, we will need to accrue a total of 130 patients to this study.

The targeted cancer survivorship groups are well represented among the CCCWFU Research Base membership. Recruiting to this protocol should be quite feasible, given the level of interest in smoking cessation among cancer survivors. A survey of Research Base sites regarding the proposed concept was conducted and twelve CCOPs responded. Estimated accrual by those 12 CCOPs was 454 patients per year meeting the proposed eligibility criteria). Extending these accrual estimates to our entire Research Base, even if only one in ten potentially eligible patients is enrolled on study, we should be able to complete accrual within 18 months.

12.3 Randomization and Stratification

Patients will be stratified by gender and assigned with equal probability to memantine or placebo using random permuted block randomization. Block sizes will be chosen randomly to ensure that future assignments cannot easily be inferred from previous assignments. Analyses will not be done separately by strata.

12.4 Analysis

The one-week abstinence rates will be measured every two weeks for the 12 weeks of the trial. The primary outcome will be the self-reported smoking cessation rate at 12 weeks. The observed rates (number abstinent divided by the number evaluable) will be compared and the subsequent large-scale smoking cessation intervention will only be undertaken if the one-week abstinence rate at 12 weeks is greater for the memantine group than for the placebo group. Exact 95% CIs will be calculated for the abstinence rate in each arm and an approximate 95% CI will be calculated for the difference in abstinence rates (providing a preliminary estimate of the treatment effect). Logistic regression will be used to assess the effect of treatment and patient characteristics on one-week abstinence at 12 weeks. Pair-wise interactions between treatment and the patient characteristics will be assessed. The main effects and interactions will assist us in determining the need for additional strata or possible changes in the eligibility criteria. A repeated measures logistic model fitted using estimating equations will be used to assess the change in abstinence over time and to assess the effect of patient characteristics on this change. These analyses will be done for both the self-report and urine cotinine confirmed measures of abstinence. Repeated measures longitudinal models will be used to assess changes over time in QoL and the number of cigarettes smoked and to assess the effect of patient characteristics on these changes. Regression diagnostics, residual plots, and exploratory analyses will be done to find appropriate transformations to satisfy the linearity, homogeneity of variances, and normality assumptions. We plan to use an unstructured covariance matrix in the repeated measures models, though other structures will be assessed and compared using likelihood ratio or BIC statistics.

12.5 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of memantine, and toxicities will be quantified using the CTCAE version 4.03 criteria.

12.6 Evaluation of Response

All patients, including though who are non-adherent, those who drop-out early, and those with protocol deviations will be included in the longitudinal analyses used to estimate the treatment effect and its 95% CI. Pair-wise interactions between treatment and the patient characteristics will be assessed. The main effects and interactions will assist us in determining the need for additional strata or possible changes in the eligibility criteria. Secondary analyses of the adherent patients will be done to provide an estimate of the treatment effect under the best possible scenario. Sensitivity analyses under various assumptions will be done to assess the possible impact the missing data could have on our conclusions.

12.7 Interim Analysis

No interim analyses for efficacy or futility are planned for this pilot study. However, safety and feasibility data, including accrual, from this trial will be reviewed twice yearly by the CCCWFU DSMB. If accrual is less than 1/3 expected after one year or 2/3 expected after two years, we will implement a study-wide conference call to discuss barriers to accrual and possible remedies. A summary of the conference call discussion will be provided to the DSMB for their consideration.

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