Title: NAC for Treating Comorbid PTSD and SUD
Informed Consent Documents
ID: Pro00052757

Medical University of South Carolina

CONSENT TO BE A RESEARCH SUBJECT

Glial Regulators for Treating Comorbid Posttraumatic Stress Disorder and Substance Use Disorders

A. Purpose and Background

You are invited to take part in a research study being sponsored by the United States Department of Defense and the Institute for Translational Neuroscience at the University of California, San Francisco. You are being invited to take part in this study because you are between 18-75 years of age, may have an alcohol or substance use disorder and symptoms of posttraumatic stress disorder (PTSD). The investigator in charge of this study is Dr. Sudie Back at the Medical University of South Carolina (MUSC). This study is being conducted in Charleston, SC and will involve approximately 90 participants.

Please read this consent form carefully because it explains what to expect with this study. Feel free to ask any questions now, or at any time during this study. All study procedures for this study will take place at MUSC. However, you may also be asked to sign a consent form for the VA if you are a patient there and the initial contact for this study took place at the VA.

The purpose of this study is to determine whether Cognitive Behavior Therapy combined with a dietary supplement called N-acetylcysteine (NAC) is effective in reducing alcohol/drug use severity and PTSD symptoms. In addition, there is a neuroimaging portion of this study which will involve the first 40 participants who are 21-40 years of age and interested in participating.

NAC has been approved by the US Food and Drug Administration (FDA) in an inhalant form for the treatment of chronic lung conditions. It is also FDA-approved in a liquid and intravenous (IV) form to treat people who have overdosed on acetaminophen (Tylenol® and other names). Thousands of patients world-wide have used this form of NAC for the treatment of acetaminophen overdose. You will receive either NAC or placebo in a capsule. Because NAC is not approved by the FDA for treating substance use disorders or PTSD, it is called an investigational drug.

B. Procedures

This study will include a 1 to 2 week screening period followed by an 8-week medication phase. During the medication phase you will be asked to come into the clinic for 1 visit each week. We will also ask you to come back to the clinic for follow-up visits about 1 and 3 months after you finish the medication.

If there is anything that makes it difficult for you to come to MUSC, you may choose to do your study visits and therapy sessions via home-based telehealth (HBT) (weeks 1, 2, 3, 5, 6, & 7 only; sessions 4 and 8 will require an in-person visit). HBT allows a therapist and patient who are not in the same room together to communicate. This is usually done over the computer using MUSC-approved teleconferencing applications. In order to complete sessions via HBT, you will need to have internet or cellular access in your home and a computer, tablet, or smartphone capable of accessing the internet. If needed, a webcam can be provided for the duration of the study. Barriers to being unable to come to MUSC for face to face treatment varies, but typically involves transportation, financial, or child care issues.

Screening and Baseline Phase (1 to 2 weeks)

During the 1 to 2 week screening phase, you will be asked questions about, for example, your age, employment, relationship status, and education. Prior medications will be recorded and a psychiatric evaluation will be done which will assess symptoms of PTSD and other psychiatric conditions in order to determine if you are eligible for the study. You will be also asked questions about your use of alcohol and drugs. A history and physical examination will be conducted, as well as an alcohol breathalyzer test, urine drug screen test, and pregnancy test (for women). If your pregnancy test is positive, your participation in this study will end and no further testing will be done.

Participant Enrollment

At the end of the screening period a medical clinician will determine if you are able to participate in the study. Therefore, even if you signed the consent form you may not be able to participate in this study. If you are eligible to continue you will be enrolled into the medication phase.

Medication Phase (8 weeks)

During this phase you will be given in random order (like the flip of a coin) either NAC 2400mg/day or placebo (a pill without medication). Neither you nor the study staff seeing you will know if you are taking NAC or placebo. Only the pharmacist who prepares the medication will know if you are on NAC or placebo until the entire study is over. You will be given capsules to take daily during the 8 weeks. All capsules will include riboflavin, a vitamin supplement which may cause your urine to be orange in color. This allows the investigators to be sure you are taking the medication. If you are already taking a multi-vitamin with riboflavin in it at the beginning of the study, you will be asked to stop taking the multi-vitamin and the study will give you a multi-vitamin that does not contain riboflavin.

You will be given a 1-week supply of medication or placebo at the beginning of each week, typically on Monday or Tuesday, and will be asked to self-report at home on a calendar the daily timing of capsules taken and bring back the form and any unused capsules at the next visit.

You will be asked to come to the clinic or meet via telehealth once a week during the medication phase. You will meet with a study team member on a weekly basis to monitor your health, side effects and use of other medications. Pregnancy tests for women will be done monthly during this phase. Should your pregnancy test be positive, this will end your participation and no further testing will be done. The weekly clinic visits will last about 1.5-2.5 hours and consist of a breathalyzer/saliva test, self-report questionnaires about alcohol/drug use, PTSD and mood, and a therapy session. Telehealth participants will be required to complete the saliva alcohol test in front of the camera (test strip held on tongue for ten seconds) which will allow a study team member to assess and validate test results. During the treatment phase you will complete 8 individual therapy sessions. These therapy sessions will involve helping you identify and change unhelpful thoughts and behaviors related to alcohol/drug use. The therapy in this research study will be in individual format and will be conducted by a well-trained clinician working under the supervision of project investigators who are clinical psychologists and medical doctors.

At the end of the medication phase (week 8), you will stop taking the study medication. No additional study medication will be given.

Follow-up Phase

You will be asked to return to the clinic or meet via telehealth about 1 and 3 months after the medication phase for questionnaires, assessment of substance use and PTSD symptoms, and alcohol breathalyzer/saliva and urine tests. You will not receive study medication during the follow-up phase. You will also be asked to report any side effects, such as dizziness and headaches, you may have had since your last clinic visit. If you cannot be reached directly for this follow-up visit, attempts will be made to reach you by contacting people identified by you in your locator form. This will only be done to verify your physical well-being and safety.

Neuroimaging Portion of the Study

If you choose to participate in the neuroimaging (i.e., brain scan) portion of the study, you will be asked a series of questions regarding the presence of metallic items in or on your body and about any brain injuries. If you are eligible to participate in the scanning session, you will be scheduled for 2 magnetic resonance imaging (MRI) scanning sessions – the first will be before you begin taking the study medication and the second will be during the final week (week 8) of taking the study medication. You will be asked to meet the study personnel at the Center for Biomedical Imaging (CBI) at 30 Bee Street, which is on the MUSC campus, for the neuroimaging visits.

The neuroimaging sessions will last approximately 1.5 hours each. When you arrive, you will be asked the same series of

questions regarding the presence of metallic items in your body. If you are female, you will also be asked to provide a urine sample for a pregnancy test. If you are pregnant, or if there are any metallic items in your body that prevent safe MRI scanning, you will not be eligible to participate further in the MRI portion of this investigation.

The MRI is a large doughnut shaped machine. You will be given earplugs to wear while you are in the scanner. You will be able to speak to and hear the research staff during the scan. We will first ask you to lay still and close your eyes while we take images of the structure of your brain. Following the structural images, we will acquire functional images of your brain activity while you listen to recordings describing your recent experiences with alcohol/drugs, a traumatic event, and neutral cues. The same procedures will be followed during the first and the second neuroimaging visits.

If you are 21-40 years old, please initial by your choice below:

____ Yes, I would like to participate in the neuroimaging visits.

____ No, I do not want to participate in the neuroimaging visits.

____ N/A, I am not between the ages of 21-40.

C. Duration

The total time in the study will be approximately 22 weeks consisting of:

1) The screening and baseline phase takes 1 to 2 weeks. You will be asked to come in for up to 3 visits during this phase with the first visit lasting about 3 to 4 hours (assessment to determine eligibility to participate in the study), the second lasting about 1.5 hours (neuroimaging scan) and the third visit (medication start) lasting about 1 hour.

2) The medication phase will last 8 weeks. During this phase, you will be asked to come to the clinic once a week or meet via telehealth for visits lasting about 1.5-2.5 hours. The longer visit during week 4 and week 8 will take about 2.5 hours because of additional questionnaires during those visits and will require coming into the clinic. The final neuroimaging scan will take place during week 8 of the treatment phase and will last about 1.5 hours.

3) The follow-up phase involves visits at 1 and 3 months after you stop taking the medication. These visits should take about 1.5 to 2 hours to complete.

D. Possible Discomforts and/or Risks

You will have to take time to come to the clinic or meet via telehealth during the screening, medication and follow-up phases of the study. Therefore, being in this study may cause inconvenience in your schedule at times. Some of the questions about your personal life, substance use, or PTSD symptoms may embarrass you or cause you distress or boredom.

You may have some side effects from the study medication. The side effects most common in people who take NAC by mouth include nausea, headache, vomiting and diarrhea. These side effects are usually mild and go away even with continued use of NAC by mouth. In this study, NAC will only be given by mouth. In addition to the side effects listed above, a skin rash has happened in about 10% of subjects participating in previous studies. If you develop a rash, you will be removed from the study medication and will be looked at by a study physician. You may, if necessary, be treated with an antihistamine (example: Benadryl) or another medication to help out with the rash.

It is highly unlikely (probably less than one chance in several thousand) that you will have a severe allergic reaction to the NAC. If you have trouble breathing, the emergency medical system (EMS - call 911) should be called, and you should be transported to the nearest emergency room for immediate treatment. Because NAC has not been studied in combination with very many other medications, it will be important for you to report to the research staff any medications you may be

taking before, during, or after the medication phase. Medications include prescription medications from a doctor, over-the-counter medications that you may buy in a drug store, herbal medications that you may buy in a health-food store, or "street" drugs.

There are known psychological risks associated with withdrawal from many substances of abuse including increased sleepiness, unhappy mood, craving, and irritability.

You will be asked to answer questions about your substance use, legal history and lifestyle. The risk of release of this sensitive, confidential information will be kept to a minimum by storing your information in locked cabinets that are in locked offices. The research staff that will be working with you has been thoroughly trained to keep your information confidential.

There is a chance that you will receive a placebo pill (a pill without medication) instead of the study medication. There is a chance that NAC or placebo may not reduce your desire to use alcohol/drugs or your PTSD symptoms. There is also a chance that your alcohol/drug use or PTSD symptoms may worsen while you are in this study. The research or procedures may involve risks that are currently unforeseeable but your health will be monitored closely to minimize the possibility of side effects.

The safety of NAC in pregnancy and in nursing mothers is unknown. Therefore, all women will be given a urine pregnancy test during screening and monthly during the medication phase. No pregnant women or nursing mothers may be in this study. Women must use a medically acceptable form of birth control while participating in the study. Acceptable forms of birth control are: an oral contraceptive (birth control pills), diaphragm or a condom used with a spermicide, intrauterine progestive contraceptive system (Progestacert®), levonorgestrel implant (Norplant®), medroxyprogesterone (Depoprovera®) injection contraception, surgical sterilization, or complete abstinence from sexual intercourse during the entire study. If you become pregnant during the study, you will be taken off the study medication and your participation in the study must end. If you wish, you will be referred for regular clinical treatment. If you become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or possibly be jailed.

Potential risks of Neuroimaging:

The risk from MRI is low. No radiation or x-rays are used in making pictures of your brain during the MRIs. You cannot have an MRI scan if you have metal in the skull, metal implants, a cardiac or brain pacemaker, or old metal fragments in the eye or retina. If you have a question about metal in your body, you should inform the researchers and they will determine whether it is safe in an MRI scanner. Some discomfort may occur from having to remain still for a while in the scanner. There is no exposure to ionizing radiation, nothing will be injured, and no blood will be taken. The MRI scanner is noisy, and there is a risk of hearing damage if you do not wear earplugs. To eliminate this risk, you will be given earplugs to wear during each scan.

Although the MRI scanner is open on both ends, some people become anxious when entering the MRI scanner due to the feeling of being enclosed. If this has happened to you in the past, you should inform the study personnel. To address this concern, all participants will be given an emergency call button which they can activate at any time during the scan if they are feeling uncomfortable in the MRI scanner. If this indicator is activated the study personnel will come into the scanning room immediately and take you out of the scanner.

E. Possible Benefits

There are no guarantees that you will directly benefit from taking part in the study. Based on experience with NAC and cognitive behavioral therapy in patients with similar disorders, researchers believe it may be of benefit to people with your conditions. Of course, because people respond differently to medications and behavioral therapies, no one can know in advance if it will be helpful for you. Being in this research study may reduce your alcohol/drug use and PTSD symptoms,

and it may also help in the understanding of how safe and effective NAC is in treating these conditions. Another benefit is that the information gained from the study will help increase our knowledge about how to best treat individuals with PTSD and substance use disorder.

F. Cost of Participation

You will not be charged for any of the study treatments or procedures. The costs of medication and all tests associated with this study and all visits will be covered by the study. Your normal data and usage rates will apply if you choose to use a cellular phone or cellular data enabled device for telehealth sessions.

G. Payment to Participants

You will be compensated for providing data and for your time while in this research study. You will receive $50 for the baseline visit, $50 for each imaging visit, and up to $40 for each weekly visit ($20 study visit, $20 therapy session). You will also receive $75 for each follow-up visit at 1 and 3 months after treatment. Thus, the total amount you may receive for your study participation is $755. Compensation can be provided by cash (in-person pick up only), gift card (in-person pick up only), or check (requires mailing address and full social security number, may take 4-6 weeks to arrive).

Telehealth participants will be offered compensation for travel to and from the three mandatory in-person visits (Baseline, Week 4, & Week 8). Also, if the baseline visit is four hours or longer, telehealth participants will be offered a meal.

Referrals

You are invited to participate in the recruitment of other subjects for this study. If you choose to participate, we will provide you with cards that you may give to other people (e.g., friends, acquaintances) who you think would be eligible and interested in this study. You may choose to tell people to whom you give these cards to call the study office if they are interested in participating in the study. These individuals will not be identified unless they contact the study office themselves. If any of the cards you are given result in successful study recruitment, you will receive $10 for each referred individual who enrolls in the study. Participation in the recruitment process is completely voluntary and if you elect not to participate, your participation in this study will not be affected in any way.

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a form 1099.

H. Alternatives

If you do not want to be in this study, other ways of treating substance use problems and PTSD are individual or group counseling, as well as several FDA approved medications. If you would like, we will refer you to clinical treatment. You will be responsible for the costs of treatment.

Withdrawal from the Study

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should talk with the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled. The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions. If your participation is ended for medical reasons, you will be referred to a doctor or other health professional for care. You will be responsible for the cost of these services.

I. Disclosure Of Results

You may request to receive a report of the aggregate results following completion of the study.

J. New Information
If there are significant new findings during the course of the study, you will be notified. These new findings include, but are not limited to, changes in the potential risks or benefits resulting from being in the research or new alternatives to being in this study, which might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue taking part in this study will be re-obtained.

K. Release Of Medical Records To Anyone Other Than The Investigators
If for any reason you would like your study records released to anyone other than the investigators, you will be asked to sign an additional release of information form. You will also be asked to sign a Health Insurance Portability and Accountability Act (HIPAA) Authorization to use or disclose your protected health information for research purposes.

L. Student Participation
Your participation or discontinuance will not constitute an element of your academic performance nor will it be part of your academic record.

M. Employee Participation
Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be part of your employee record.

N. Invitation To Participate In Future Studies
In the future, MUSC may be conducting other related studies. Please let us know your interest in being re-contacted in the future by telephone, mail or email about other studies that you may qualify for:

____ Yes, I am interested in being contacted about future studies.

____ No, I am not interested in being contacted about future studies.

O. Clinical Trial Registry Databank
A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

P. Sponsor Commitment Section
The Department of Defense will not pay for any medical treatment in the event of a study related injury.

Q. Contact
You have the option of receiving appointment reminders and links to study surveys through text messages. Should you elect to receive text messages, normal cellular data usage and rates will apply. Please indicate your choice below:
____Yes, I agree to be contacted via text message
____No, I do not agree to be contacted via text message

Confidentiality:
We will take careful precautions to maintain your confidentiality, using procedures that we have successfully employed in similar previous as well as ongoing studies. All study data related to psychological outcomes (i.e., the responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be a master list of participants (again, not linked to any participant responses) which will be kept separate from all data and will be available only to Dr. Back and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or Research Assistant's office). Access to research records (paper and computerized) will be restricted to the project staff, sponsor audit personnel, VAMC R&D auditors, and MUSC IRB auditors. Neuroimaging data will be stored on a secure password protected server maintained by MUSC's Center for Biomedical Imaging (CBI). Only Dr. Back and approved study personnel will have access to the files on the secure CBI server.

CONSENT

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that you are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact Dr. Sudie Back at (843) 792-9383. I may contact the Medical University of SC Hospital Medical Director (843) 792-9537 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date

Subject's Name: **Date:**

Principal Investigator: Sudie E. Back, Ph.D.

Study Title: **Glial Regulators for Treating Comorbid Posttraumatic Stress Disorder and Substance Use Disorders**

A. Purpose and Background

You are invited to take part in a research study sponsored by the United States Department of Defense and the Institute for Translational Neuroscience at the University of California, San Francisco. You are being invited to take part in this study because you are a Veteran between 18-75 years of age who may have a substance use disorder and symptoms of posttraumatic stress disorder (PTSD). The investigator in charge of this study is Dr. Sudie Back at the Medical University of South Carolina (MUSC) and the Ralph H. Johnson Veteran's Medical Center (VAMC). This study is being conducted in Charleston, SC and will involve approximately 90 participants.

Please read this consent form carefully because it explains what to expect with this study. Feel free to ask any questions now, or at any time during this study. The study procedures for this study will take place at the VAMC and MUSC.

The purpose of this study is to determine whether Cognitive Behavior Therapy combined with a dietary supplement called N-acetylcysteine (NAC) is effective in reducing alcohol/drug use severity and PTSD symptoms. In addition, there is a neuroimaging portion of this study which will involve the first 40 participants who are 21-40 years of age and interested in participating.

NAC has been approved by the US Food and Drug Administration (FDA) in an inhalant form for the treatment of chronic lung conditions. It is also FDA-approved in a liquid and intravenous (IV) form to treat people who have overdosed on acetaminophen (Tylenol® and other names). Thousands of patients world-wide have used this form of NAC for the treatment of acetaminophen overdose. Because NAC is not approved by the FDA for treating substance use disorders, it is called an investigational drug.

B. Procedures

This study will include a 1 to 2 week screening period followed by an 8-week medication phase. During the medication phase you will be asked to come into the clinic for 1 visit each week. We will also ask you to come back to the clinic for follow-up visits about 1 and 3 months after you finish the medication.

If there is anything that makes it difficult for you to come to the Ralph H. Johnson VA, you may choose to do your study and therapy sessions via home-based telehealth (HBT) (weeks 1, 2, 3, 5, 6, & 7 only; weeks 4 & 8 will require an in-person visit). HBT allows a therapist and patient who are not in the same room together to communicate. This is usually done over the computer using VA-approved teleconferencing software. In order to complete sessions via HBT, you will need to have high speed internet access in your home and a computer or tablet capable of downloading VA-approved videoconferencing software. If needed, a webcam can be provided for the duration of the study. Barriers to being unable to come to the VA for face to face treatment varies, but typically involves transportation, financial, or child care issues.

Screening and Baseline Phase (1 to 2 weeks)

During the 1 to 2 week screening phase, you will be asked questions about, for example, your age, employment, relationship status, and education. Prior medications will be recorded and a psychiatric evaluation will be done which will assess symptoms of PTSD and other psychiatric conditions in order to determine if you are eligible for the study. You will be also asked questions about your use of alcohol and drugs. A history and physical examination will be conducted, as well as an alcohol breathalyzer test, urine drug screen test, and pregnancy test (for women). If your pregnancy test is positive, your participation in this study will end and no further testing will be done.

Participant Enrollment

At the end of the screening period a medical clinician will determine if you are able to participate in the study. Therefore, even if you signed the consent form you may not be able to participate in this study. If you are eligible to continue you will be enrolled into the medication phase.

Medication Phase (8 weeks)

During this phase you will be given in random order (like the flip of a coin) either NAC 2400mg/day or placebo (a pill without medication). Neither you nor the study staff seeing you will know if you are taking NAC or placebo. Only the pharmacist who prepares the medication will know if you are on NAC or placebo until the entire study is over. You will be given capsules to take daily during the 8 weeks. All capsules will include riboflavin, a vitamin supplement which may cause your urine to be orange in color. This allows the investigators to be sure you are taking the medication. If you are already taking a multi-vitamin with riboflavin in it at the beginning of the study, you will be asked to stop taking the multi-vitamin and the study will give you a multi-vitamin that does not contain riboflavin.

You will be given a 1-week supply of medication or placebo at the beginning of each week, typically on Monday or Tuesday, and will be asked to self-report at home on a calendar the daily timing of capsules taken and bring back the form and any unused capsules at the next visit.

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The weekly visits will last about 1.5-2.5 hours and consist of a breathalyzer/saliva test, self-report questionnaires about alcohol/drug use, PTSD and mood, and an individual therapy session. Telehealth participants will be required to complete the saliva alcohol test in front of the camera (test strip held on tongue for ten seconds) which will allow a study team member to assess and validate test results. During the treatment phase you will complete 8 therapy sessions. These therapy sessions will involve helping you identify and change unhelpful thoughts and behaviors related to alcohol/drug use. The therapy in this research study will be in individual format and will be conducted by a well-trained clinician working under the supervision of project investigators who are clinical psychologists and medical doctors.

At the end of the medication phase (week 8), you will stop taking the study medication. No additional study medication will be given.

Follow-up Phase

You will be asked to return to the clinic or meet via telehealth about 1 and 3 months after the medication phase for questionnaires, assessment of substance use and PTSD symptoms, and alcohol breathalyzer/saliva tests and urine tests. You will not receive study medication during the follow-up phase. You will also be asked to report any side effects, such as dizziness and headaches, you may have had since your last clinic visit. If you cannot be reached directly for this follow-up visit, attempts will be made to reach you by contacting people identified by you in your locator form. This will only be done to verify your physical well-being and safety.

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The neuroimaging sessions will last approximately 1.5 hours each. When you arrive, you will be asked the same series of questions regarding the presence of metallic items in your body. If you are female you will also be asked to provide a urine sample for a pregnancy test. If you are pregnant, or if there are any metallic items in your body that prevent safe MRI scanning, you will not be eligible to participate further in the MRI portion of this investigation.

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If you are 21-40 years old, please initial by your choice below:

____ Yes, I would like to participate in the neuroimaging visits.

____ No, I do not want to participate in the neuroimaging visits.

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The total time in the study will be approximately 22 weeks consisting of:

1) The screening and baseline phase takes 1 to 2 weeks. You will be asked to come in for up to 3 visits during this phase with the first visit lasting about 3 to 4 hours (assessment to determine eligibility to participate in the study), the second lasting about 1.5 hours (neuroimaging scan) and the third visit (medication start) lasting about 1 hour.

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you distress or boredom.

You may have some side effects from the study medication. The side effects most common in people who take NAC by mouth include diarrhea, nausea and vomiting, and headache. These side effects are usually mild and go away even with continued use of NAC by mouth. In this study, NAC will only be given by mouth. In addition to the side effects listed above, a skin rash has happened in about 10% of subjects participating in previous studies. If you develop a rash, you will be removed from the study medication and will be looked at by a study physician. You may, if necessary, be treated with an antihistamine (example: Benadryl) or another medication to help out with the rash.

It is highly unlikely (probably less than one chance in several thousand) that you will have a severe allergic reaction to the NAC. If you have trouble breathing, the emergency medical system (EMS - call 911) should be called, and you should be transported to the nearest emergency room for immediate treatment. Because NAC has not been studied in combination with very many other medications, it will be important for you to report to the research staff any medications you may be taking before, during, or after the medication phase. Medications include prescription medications from a doctor, over-the-counter medications that you may buy in a drug store, herbal medications that you may buy in a health-food store, or "street" drugs.

There are known psychological risks associated with withdrawal from many substances of abuse including increased sleepiness, unhappy mood, craving, and irritability.

You will be asked to answer questions about your substance use, legal history and lifestyle. The risk of release of this sensitive, confidential information will be kept to a minimum by storing your information in locked cabinets that are in locked offices. The research staff that will be working with you has been thoroughly trained to keep your information confidential.

There is a chance that you will receive a placebo pill (a pill without medication) instead of the study medication. There is a chance that NAC or placebo may not reduce your desire to use alcohol/drugs or your PTSD symptoms. There is also a chance that your alcohol/drug use or PTSD symptoms may worsen while you are in this study. The research or procedures may involve risks that are currently unforeseeable but your health will be monitored closely to minimize the possibility of side effects.

The safety of NAC in pregnancy and in nursing mothers is unknown. Therefore, all women will be given a urine pregnancy test during screening and monthly during the medication phase. No pregnant women or nursing mothers may be in this study. Women must use a medically acceptable form of birth control while participating in the study. Acceptable forms of birth control are: an oral contraceptive (birth control pills), diaphragm or a condom used with a spermicide, intrauterine progestive contraceptive system (Progestacert®), levonorgestrel implant (Norplant®), medroxyprogesterone (Depoprovera®) injection contraception, surgical sterilization, or complete abstinence from sexual intercourse during the entire study. If you become pregnant during the study, you will be taken off the study medication and your participation in the study must end. If you wish, you will be referred for regular clinical treatment. If you become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or possibly be jailed.

Potential risks of Neuroimaging:

The risk from MRI is low. No radiation or x-rays are used in making pictures of your brain during the MRIs. You cannot have an MRI scan if you have metal in the skull, metal implants, a cardiac or brain pacemaker, or old metal fragments in the eye or retina. If you have a question about metal in your body, you should inform the researchers and they will determine whether it is safe in an MRI scanner. Some discomfort may occur from having to remain still for a while in the scanner. There is no exposure to ionizing radiation, nothing will be injured, and no blood will be taken. The MRI scanner is noisy, and there is a risk of hearing damage if you do not wear earplugs. To eliminate this risk, you will be given earplugs to wear during each scan.

Although the MRI scanner is open on both ends, some people become anxious when entering the MRI scanner due to the feeling of being enclosed. If this has happened to you in the past, you should inform the study personnel. To address this concern, all participants will be given an emergency call button which they can activate at any time during the scan if they are feeling uncomfortable in the MRI scanner. If this indicator is activated the study personnel will come into the scanning room immediately and take you out of the MRI.

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E. Possible Benefits

There are no guarantees that you will directly benefit from taking part in the study. Based on experience with NAC and cognitive behavioral therapy in patients with similar disorders, researchers believe it may be of benefit to people with your conditions. Of course, because people respond differently to medications and behavioral therapies, no one can know in advance if it will be helpful for you. Being in this research study may reduce your alcohol/drug use and PTSD symptoms, and it may also help in the understanding of how safe and effective NAC is in treating these conditions. Another benefit is that the information gained from the study will help increase our knowledge about how to best treat Veterans with PTSD and substance use disorder.

F. Cost of Participation

You will not be required to pay for medical care or services received as a participant in a VA research project except as follows: Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

G. Payment to Participants

You will be compensated for providing data and for your time while in this research study. You will receive $50 for the baseline visit, $50 for each imaging visit, and up to $40 for each weekly visit ($20 study visit, $20 therapy session). You will also receive $75 for each follow-up visit at 1 and 3 months after treatment. Thus, the total amount you may receive for your study participation is $755. Compensation can be provided by cash (in-person pick up only), gift card (in-person pick up only), or check (requires mailing address and full social security number, may take 4-6 weeks to arrive).

Telehealth participants will be offered compensation for travel to and from the three mandatory in-person visits (Baseline, Week 4, & Week 8). Also, if the baseline visit is four hours or longer, telehealth participants will be offered a meal.

Referrals

You are invited to participate in the recruitment of other subjects for this study. If you choose to participate, we will provide you with cards that you may give to other people (e.g., friends, acquaintances) who you think

would be eligible and interested in this study. You may choose to tell people to whom you give these cards to call the study office if they are interested in participating in the study. These individuals will not be identified unless they contact the study office themselves. If any of the cards you are given result in successful study recruitment, you will receive $10 for each referred individual who enrolls in the study. Participation in the recruitment process is completely voluntary and if you elect not to participate, your participation in this study will not be affected in any way.

The Internal Revenue Service (IRS) requires a tax form be filed if your compensation exceeds $600/year. However, if the payment for participation will be made through Austin Financial Service Center, it may generate IRS Form 1099 automatically, regardless of amount.

H. Alternatives

If you do not want to be in this study, other ways of treating substance use problems and PTSD are individual or group counseling, as well as several FDA approved medications. If you would like, we will refer you to clinical treatment. You will be responsible for the costs of treatment.

Withdrawal from the Study

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should talk with the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled. The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions. If your participation is ended for medical reasons, you will be referred to a doctor or other health professional for care. You will be responsible for the cost of these services.

I. Disclosure Of Results

You may request to receive a report of the aggregate results following completion of the study.

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J. New Information

If there are significant new findings during the course of the study, you will be notified. These new findings include, but are not limited to, changes in the potential risks or benefits resulting from being in the research or new alternatives to being in this study, which might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue taking part in this study will be re-obtained.

K. Release Of Medical Records To Anyone Other Than The Investigators

If for any reason you would like your study records released to anyone other than the investigators, you will be asked to sign an additional release of information form. You will also be asked to sign a Health Insurance Portability and Accountability Act (HIPAA) Authorization to use or disclose your protected health information for research purposes.

L. Student Participation

Your participation or discontinuance will not constitute an element of your academic performance nor will it be part of your academic record.

M. Employee Participation

Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be part of your employee record.

N. Clinical Trial Registry Databank

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

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O. Contact

You have the option of receiving appointment reminders and links to study surveys through text messages. Should you elect to receive text messages, normal cellular data usage and rates will apply. Please indicate your choice below:

____Yes, I agree to be contacted via text message

____No, I do not agree to be contacted via text message

Confidentiality:

We will take careful precautions to maintain your confidentiality, using procedures that we have successfully employed in similar previous as well as ongoing studies with Veterans. All study data related to psychological outcomes (i.e., the responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be a master list of participants (again, not linked to any participant responses) which will be kept separate from all data and will be available only to Dr. Back and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or Research Assistant's office). Access to research records (paper and computerized) will be restricted to the project staff, sponsor audit personnel, VAMC R&D auditors, and MUSC IRB auditors. Neuroimaging data will be stored on a secure password protected server maintained by MUSC's Center for Biomedical Imaging (CBI) for the purposes of this study. Only Dr. Back and approved study personnel will have access to the files on the secure CBI server.

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CONSENT

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

The VA will provide necessary medical treatment to a research subject injured by participation in a research project. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by this VA Medical Center. Financial compensation is not available for such things as lost wages, disability or discomfort due to an injury.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

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Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, or if I have comments, concerns or complaints I may contact Dr. Sudie Back at (843) 792-9383. I may contact the VA Medical Center's Medical Director at (843) 789-7200 concerning medical treatment.

If I have questions, comments, concerns or wish to voice a complaint, I may contact the VA Research Compliance Officer at (843) 789-7399.

If I have any questions about my rights as a research subject in this study I may contact the Medical University of SC Institutional Review Board for Human Research at (843) 792-4148.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date