A pilot study of N-acetylcysteine for alcohol use disorder

NCT number: NCT04964843

Document date: 10/04/2021

EIRB Protocol Template (Version 1.7)

1.0 General Information

***Please enter the full title of your study:**

A pilot study of N-acetylcysteine for alcohol use disorder

***Please enter the Protocol Number you would like to use to reference the protocol:**

NAC
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
◉	**P and R** - Uniformed Services University of the Health Sciences (USUHS)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Gray, Joshua C, PhD

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Livezey, Jeffrey Robert, LTC
Associate Investigator
Oliver, Thomas George, MD COL
Associate Investigator

B) Research Support Staff

Dufour, Steven Christopher, B.A ENS
Research Coordinator
Murphy, Mikela Alice
Research Coordinator
Rouska, Ashton
Research Coordinator
Schultz, Lauren
Research Coordinator
THOMPSON, MATTHEW
Research Coordinator

3.3 *Please add a Protocol Contact:

Gray, Joshua C, PhD

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 * Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study? If Yes, answer the questions according to the IRB/HRPP Determination.

○ Yes ◉ No

IRB Name	Review Date	Determination
No records have been added		

4.2 * Is this a research study or a Compassionate Use/Emergency Use/HUD project?

◉ Yes ○ No

4.3 What type of research is this?

- ☑ Biomedical Research
- ☑ Clinical trial (FDA regulated)
- ☐ Behavioral Research
- ☐ Educational Research
- ☑ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.4 Are you conducting this project in pursuit of a personal degree?

○ Yes ◉ No

4.6 * Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

◉ Yes ○ No

4.7 * Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

Name: (Last, First, M.I.)	Phone Number:	Email Address:	Associated Institution:
Leggio, Lorenzo Role on Protocol: Consultant, protocol design, no identifying participant information	240-478-1503	lorenzo.leggio@nih.gov	National Institutes of Health
Name: (Last, First, M.I.) Saunders, David Role on Protocol: Associate Investigator	Phone Number: 301.295.0016	Email Address: david.saunders@usuhs.edu	Associated Institution: USU

5.2 Will you have a Research Monitor for this study?

○ Yes
◉ No
○ N/A

6.0

Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
: Other USU	: Other USU new faculty startup funds	150000

Total amount of funding:

150000

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

◉ Yes ○ No

8.2 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
P&R	Uniformed Services University	Lead site	P60001	09/27/2023	: Other	: USUHS IRB #1
P&R	WRNMMC ATS Clinic	Recruitment	FWA00017749		: Other	: USUHS IRB #1
	WRNMMC					USUHS

P&R	Investigational Pharmacy	Other	FWA00017749		: Other	: IRB #1

Other:

	Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.4 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ◉ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

NAC, n-acetylcysteine, AUD, alcohol use disorder

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Alcohol abuse is responsible for 1 in 10 deaths among working age adults in the U.S. and costs ~$249 billion annually.(Stahre, Roeber, Kanny, Brewer, & Zhang, 2014) Currently approved medications for alcohol use disorder (AUD) exert only small to medium effects on drinking, with estimates indicating 12 to 20 drinkers need to be treated for one of them to benefit from the two leading medications, acamprosate and naltrexone.(Jonas et al., 2014) Thus, many patients do not benefit from current pharmacotherapies for AUD.

N-acetylcysteine (NAC) is one promising pharmacotherapy that is well-tolerated, safe, and exhibits preliminary evidence across a number of psychiatric and neurological disorders.(Minarini et al., 2017) NAC is available over the counter, has been used all over the world for a variety of conditions, most notably for its 1985 FDA approved use as an antidote for acetaminophen overdose.

The NAC dosage (3000 milligrams) was selected as most prior studies in addiction have used 2400-3000mg and even studies up to 3600mg have found it was well-tolerated (Minarini et al., 2017). Many studies using doses in this range achieved clinically significant improvements (e.g., Fernandes et al., 2016), including a study of NAC for smoking cessation which used 3000mg (Prado et al., 2015). 7 weeks was selected rather than 12 weeks or longer duration because this within the range of prior clinical trials of NAC (most are 8-12 weeks) and is fitting for the goals of this pilot trial seeking to establish feasibility and sample size for a larger clinical trial (Gray et al., 2010; Mardikian et al., 2007). It is beyond the primary aims of this study and the resources of the team to seek longer term outcomes (e.g., drinking at 6 months; **https://www.fda.gov/media/91222/download**).

Neurobiological mechanisms. NAC is an acetyl derivative of the amino acid cysteine, a precursor for the antioxidant glutathione.(Minarini et al., 2017) NACs purported utility for AUD comes from its downstream effects on neurotransmitters implicated in the development and maintenance of AUD: glutamate and dopamine. Alcohol abuse induces dysregulation of dopamine neurotransmission and enhancement of glutamatergic activity leading to alterations in reward, affect, and cognition.(Burnett, Chandler, & Trantham-Davidson, 2016) NAC enhances cystine to glutamate exchange via the x_c^- system that imports cystine inside glial cells and exports a glutamate molecule in the extracellular compartment. This may reverse addictive processes by reducing excitatory glutamatergic transmission and regulating dopamine release.(Dean, Giorlando, & Berk, 2011) Indeed, a recent rodent study found that NAC administered prior to chronic ethanol administration blocked three of the central processes: ethanol-induced behavioral sensitization (a method of studying drug-induced plasticity changes following repeated exposure(Legastelois, Botia, Coune, Jeanblanc, & Naassila, 2014)), an increase of ΔFosB (accumulation of which increases the motivational properties of alcohol) in the prefrontal cortex, and a reduction of ΔFosB in the nucleus accumbens.(Morais-Silva, Alves, & Marin, 2016)

Basic preclinical research. Findings demonstrate NAC crosses the blood-brain barrier and increases brain glutathione levels in rodents and in humans.(Reyes et al., 2016) A recent rodent investigation found that NAC reduced ethanol-reinforced responding in both a fixed and progressive ratio schedule, and it reduced reacquisition in rats abstinent for 17 days. (Lebourgeois, González-Marín, Jeanblanc, Naassila, & Vilpoux, 2017) This is further supported by previous studies that found NAC decreased withdrawal-induced anxiety and elevated corticosterone levels(R Schneider, Santos, Clarimundo, & Dalmaz, 2015) as well as ethanol intake in a two-bottle choice paradigm.(Quintanilla et al., 2016) In the latter study, ethanol intake was only reduced following chronic administration (3 months), suggesting that NAC acts by counteracting neuroadaptations produced from chronic use. Indeed, it has been found to reduce alcohol-related neuroinflammation in rodents.(Ricardo Schneider et al., 2017)

Human research. A recent review details human studies on NAC for addiction.(Morley et al., 2018) Briefly, the two trials assessing the effect of NAC on alcohol use were secondary analyses in the context of cannabis trials. The first was a randomized, placebo-controlled trial in 277 adults with cannabis use disorder finding that NAC increased abstinence from alcohol and reduced drinking.(Squeglia et al., 2018) The second was a randomized, placebo-controlled trial in 116 cannabis using adolescents, finding reductions in drinking associated with changes in cannabis use.(Squeglia et al., 2016). Several studies on the effects of NAC on nicotine dependence have reported less nicotine craving, higher abstinence rates, and reduction in daily smoking (Gómez-Coronado, Walker, Berk, & Dodd, 2018).

With regard to clinical studies of NAC for other addictions, there have been three larger randomized controlled trials of NAC to date (Ns > 110). NAC reduced cannabis use in adolescents,(Gray et al., 2012) but had no effect in adults.(Gray et al., 2017) Furthermore, NAC reduced relapse in individuals with cocaine dependence, but only in the subset of patients that were initially abstinent.(LaRowe et al., 2013) Despite promising human studies, no prospective investigations to date have focused on NAC with alcohol use as the primary aim or on treatment-seeking drinkers.

Potential mechanisms. NAC may be particularly well-suited to treat some neuropsychiatric conditions that co-occur with drinking. Specifically, human and rodent studies identified beneficial effects of NAC on anxiety(Costa et al., 2017) and a meta-analysis found that NAC reduces depression and improves functionality.(Fernandes, Dean, Dodd, Malhi, & Berk, 2016) Given the influence of negative affect and stress on alcohol use,(Sinha et al., 2011) a reduction in these symptoms may also lead to better drinking outcomes.

Preliminary work has explored the effect of NAC on cognition. Preliminary findings suggest NAC may impact response inhibition(Schulte et al., 2018) and reduce cocaine attentional bias in individuals with cocaine use disorder.(Levi et al., 2017) Furthermore, NAC appears to improve cognition in individuals with schizophrenia.(Breier et al., 2018) Given the consistent association of a wide array of cognitive functions with AUDs,(Stavro, Pelletier, & Potvin, 2013) replication of these effects of NAC in individuals with AUDs may support potential mechanisms of its therapeutic effect.

9.3 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions /hypotheses

The primary aim of the current study is to establish feasibility, dropout rate, and estimate the standard deviation of the outcome measures in order to estimate the required sample for a fully powered clinical trial and to refine the final measures for use in the fully powered clinical trial. The secondary aim is to explore preliminary efficacy signal of NAC. Specifically, we have primary, secondary, and tertiary hypotheses related to the putative effects of NAC**:** 1) NAC will reduce total drinking days and drinks per drinking day; 2) NAC will reduce alcohol cue-reactivity, alcohol demand on the alcohol purchase task (i.e., a measure assessing preferences for alcohol across a range of prices to determine the relative reinforcing value of alcohol), and trait-based craving; and 3) NAC will lead to improvements in response inhibition, working memory, prcoessing speed, and executive functioning; and reductions in depression symptoms and anxiety symptoms. We will also explore change in total marijuana use days, total cigarette use days, and cigarettes per day in the subsets of individuals who use marijuana and cigarettes.

We anticipate this study will take 2 years to complete following approval (enrolling approximately 1 participant every other week).

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

Double-blind, randomized, placebo-controlled, pilot study

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Adult Military Healthcare Beneficiaries enrolled in an outpatient AUD treatment program at a MTF.

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

At-risk alcohol use increases risk for and impedes recovery from numerous conditions common to deployed military members including depression, posttraumatic stress disorder (PTSD), trauma tic brain injury (TBI), and suicidality. Furthermore, it is associated with a myriad of health consequences including cancer, cardiovascular events, injuries, and violence. Military members drink even greater quantities of alcohol than their same-age peers in the general population, and high rates of binge drinking and at-risk use pose threats to overall troop readiness.

Many patients do not significantly benefit from current pharmacotherapies for AUD. NAC is one promising pharmacotherapy that is well-tolerated, safe, and exhibits preliminary evidence across a number of psychiatric and neurological disorders. This study will be an important step forward in determining if NAC is a potential treatment for AUD.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Individuals will be recruited from the Addiction Treatment Services center at WRNMMC. Specifically, the study team will post flyers on tables around ATS and will provide ATS staff with study flyers and a description of the research study. Preexisting patients as well as new patients will be informed of the study by ATS staff and provided a flyer. The ATS staff have agreed to mention the study both in individual and group settings (IOP). Study staff may also come to discuss the research study as requested by ATS. The study will typically be discussed with patients on the day of their intake. They will inform patients that it is a 7-week clinical trial of an experimental medication for AUD taking place at USU on base. It will not interrupt their current treatment and thus they can participate while in treatment at ATS. Given the exclusion criteria, focus will be on patients who have not opted to take an FDA approved medication for AUD. The ATS providers will wait to verbally inform patients about the study until after they have had an opportunity to be evaluated and recommended for FDA approved medication for AUD (e.g., naltrexone). Only those that are not taking FDA approved medications will be enrolled in the study. If they change their mind after enrolling in the study and want to take an FDA approved medication we will encourage them to discuss with their provider and follow their clinical recommendations. This will not impact their participation in the study and we will control for it statistically in our analysis.

Interested individuals will contact the research team and be screened over the phone for eligibility, then eligible participants will be scheduled for their baseline visit, ideally 1-3 weeks after the phone screen. Phone screening procedures are outlined in the table in 10.2. All in-person visits will take place at buildings 17 and 53 of the Uniformed Services University. 1-2 days prior to each scheduled appointment, participants will be called to confirm the appointment and screened for COVID symptoms. If any COVID symptoms are endorsed, they will be rescheduled and told to get tested for COVID and see their primary care provider (see NAC COVID screen and COVID screen phone call docs for additional details).

Below are brief descriptions of the procedures for each study session (for a detailed description of the study protocol and assessments see "NAC script" and "NAC assessments" attachments, respectively):

Baseline Visit (Wk 0)
Participants will be temperature checked with a non-contact thermometer and screened for COVID symptoms. If their temperature is 100.4°F and above or they endorse any of the COVID symptoms, they will be rescheduled and told to get tested for COVID and see their primary care provider. Participants will be administered a breathalyzer by the research assistant (RA) to check BAC. If BAC is > 0, the RA will wait a few minutes and readminister. If BAC is 0, the RA will proceed with the study. If BAC is between .01 and .049, the RA will have the participant wait until it drops to 0. If the participant refuses to wait, the research team will reschedule their appointment and the participant can leave. If BAC is $\geq$.05, the participant will be transported to the WRNMMC emergency department to assess alcohol withdrawal. If the participant refuses to go to the emergency department, they will be informed that the research team will be forced to contact the NSA Bethesda police ((301) 295-1246) out of concern for their safety. A member of the study team will walk the participants unless by the judgement of the research assistant, the participant is unable to walk unassisted. In this case, we will contact 911 to dispatch a team to evaluate the participant and transport them as needed to the WRNMMC ED.

Participants with a BAC of 0 will complete the informed consent process. They will undergo a physical exam by the physician. During the physical, female participants will undergo a pregnancy screen using a pregnancy test kit. If the screen is positive, they will be told they are not eligible to participate and they will not be counted in the study's enrollment number. Further, they will be instructed to contact their primary care provider to confirm the results and discuss the risks of alcohol use during pregnancy. Next, the RA will conduct the MADRS interview, then participants will complete the TLFB self-report form. They will then complete the computer questionnaires (demographics, ASSIST, AUDIT, APT, PACS, DDT, SIAS-6, SPS-6, e-cigarette questions, HONC, GAD-7, mental health services, medications and supplements, and military service questions) and behavioral tasks (Stop Signal, N-back, and Trail Making). Participants will be asked the treatment questions and referred to mental health resources by the RA. They will then be scheduled for their next study session and complete payment paperwork with the RA. Then they will be randomized to either 7 weeks of oral NAC (3000 milligrams) or 7 weeks of placebo. We will advise participants to inform their provider of participating in this research study and of taking 3000mg NAC or placebo. Participants will be given a business card to give to their provider stating they are in the study and taking 3000mg of NAC or placebo. Participants will be instructed to go to the Investigational Pharmacy (building 9) immediately after their appointment to pick up their study medication. They will be escorted by the RA if they have never been before or don't remember how to get there. The pharmacy will handle gender stratified randomization. The first study session will take approximately 3 hrs to complete.

In-person visits (Wk 1, 3, and 5)

Participants will be temperature checked with a non-contact thermometer and screened for COVID symptoms. If their temperature is 100.4°F and above or they endorse any of the COVID symptoms, they will be rescheduled and told to get tested for COVID and see their primary care provider. Participants will be administered a breathalyzer by the research assistant (RA) to check BAC. If BAC is > 0, the RA will wait a few minutes and readminister. If BAC is 0, the RA will proceed with the study. If BAC is between .01 and .049, the RA will have the participant wait until it drops to 0. If the participant refuses to wait, the research team will reschedule their appointment and the participant can leave. If BAC is ≥.05, the participant will be transported to the WRNMMC emergency department to assess alcohol withdrawal. If the participant refuses to go to the emergency department, they will be informed that the research team will be forced to contact the NSA Bethesda police ((301) 295-1246) out of concern for their safety. A member of the study team will walk the participants unless by the judgement of the research assistant, the participant is unable to walk unassisted. In this case, we will contact 911 to dispatch a team to evaluate the participant and transport them as needed to the WRNMMC ED.

Female participants will be asked by the physician if they believe there's been a change to their pregnancy status since their last appointment. If they believe there has been a change, they will undergo a pregnancy screen using a pregnancy test kit, administered by the physician. If the screen is positive, they will be told they are no longer eligible to participate. Further, they will be instructed to contact their primary care provider to confirm the results and discuss the risks of alcohol use during pregnancy. The physician will then assess the participant for adverse events with the SAFTEE.

Next, the RA will conduct the pill counts, MADRS interview, then participants will complete the TLFB self-report form. Participants will then complete the computer questionnaires (APT, PACS, DDT, SIAS-6, SPS-6, and GAD-7) and behavioral tasks (Stop Signal, N-back, and Trail Making). These study sessions will take approximately 2 hrs to complete.

- During week 3 only: they will complete the alcohol cue reactivity procedure and alcohol urge questionnaire administered by the RA. These tasks will utilize a virtual reality bar lab (technology and software details in 10.2) to simulate a bar experience. Participants will first be screened to assess if they are safe to complete the task as outlined in the script. If they fail the screening, the RA will move to the next section of the script. If they pass the screening, the RA will show them how to use the headset and controllers and help them put on the headset. The RA will then launch the task for them to complete. The virtual reality scenarios will include bar scenes and other scenes with drinking alcohol. Some sample images are provided in the "VR images" document. Participants will be instructed that if they feel any discomfort during the task, they should remove the headset immediately. In these cases, the RA will move to the next section of the script. These tasks will take about 10 to 30 minutes to complete. Week 3 study session will take approximately 2.5 hrs to complete.

Participants will be asked the treatment questions and referred to mental health resources by the RA. They will then be scheduled for their next study session by the RA.

During weeks 1 and 3 only: Participants will be instructed to go to the Investigational Pharmacy (building 9) immediately after their appointment to pick up their study medication. They will be escorted by the RA if they don't remember how to get there. If a participant misses an appointment, they will also be asked to pick up the medication at week 5.

Phone calls (Wk 2, 4, and 6)
Participants will be assessed with the adverse event open-ended questions and will complete the TLFB self-report form, then will be scheduled for their next study session. Phone calls will last approximately 30 mins.

Final Visit (Wk 7)
Participants will be temperature checked with a non-contact thermometer and screened for COVID symptoms. If their temperature is 100.4°F and above or they endorse any of the COVID symptoms, they will be rescheduled and told to get tested for COVID and see their primary care provider. Participants will be administered a breathalyzer by the research assistant (RA) to check BAC. If BAC is > 0, the RA will wait a few minutes and readminister. If BAC is 0, the RA will proceed with the study. If BAC is between .01 and .049, the RA will have the participant wait until it drops to 0. If the participant refuses to wait, the research team will reschedule their appointment and the participant can leave. If BAC is ≥.05, the participant will be transported to the WRNMMC emergency department to assess alcohol withdrawal. If the participant refuses to go to the emergency department, they will be informed that the research team will be forced to contact the NSA Bethesda police ((301) 295-1246) out of concern for their safety. A member of the study team will walk the participants unless by the judgement of the research assistant, the participant is unable to walk unassisted. In this case, we will contact 911 to dispatch a team to evaluate the participant and transport them as needed to the WRNMMC ED.

The physician will assess the participant for adverse events with the SAFTEE. The RA will conduct the pill counts, MADRS interview, and then participants will complete the TLFB self-report form. Participants will complete the computer questionnaires (APT, PACS, DDT, SIAS-6, SPS-6, GAD-7, and Treatment guess) and behavioral tasks (Stop Signal, N-back, and Trail Making). Participants will be asked the treatment questions and referred to mental health resources by the RA. The final visit will take approximately 2 hrs to complete.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

Self-report:

1. **Demographics:** We will ask age, sex, years of education, ethnicity/race, weight, height, marital status, college student status, employment status, and pretax household income. Duration: 2 minutes.
2. **Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).** A measure of current, recent, and lifetime drug use, which has been modified to remove redundant questions regarding alcohol and smoking. Duration 3 minutes. (Humeniuk, Henry-Edwards, Ali, Poznyak, & Monteiro, 2010).
3. **Alcohol Use Disorder Identification Test (AUDIT).** A 10-item measure of alcohol use and misuse. Duration: 2 minutes. (Saunders, Aasland, Babor, De La Fuente, & Grant, 1993)
4. **Alcohol Purchase Task (APT).** 17 item measure assessing preferences for alcohol at various prices. Duration 3 minutes. (Kaplan et al., 2018)
5. **Penn Alcohol Craving Scale (PACS):** The PACS is a 5-item measure of craving for alcohol over the past week. Each item is rated on a scale from 0 to 6. This self-report form takes approximately 3 minutes to complete. (Flannery, Volpicelli, & Pettinati, 1999)
6. **Delayed Discounting Task (DDT).** This task assesses capacity to delay gratification. Duration: 3 minutes. (Kirby et al., 1999)
7. **Social Interaction Anxiety Scale (SIAS-6) and Social Phobia Scale (SPS-6):** 12-item measure on social anxiety and social phobia. Duration: 3 minutes. (Peters, Sunderland, Andrews, Rapee, & Mattick, 2012)
8. **TLFB alcohol/cigarette/marijuana use.** Asks clients to retrospectively estimate their daily alcohol, cigarette, and marijuana consumption over a time period ranging from 7-30 days (on the first meeting) via a self-report form. Duration: 5 minutes. (Sobell & Sobell, 1996)
9. **E-cigarette questions:** "Have you ever used an electronic nicotine product, even one or two times? Do you now use electronic nicotine products?" Duration: 1 minute. (not specifically based on any preexisting measure).
10. **Hooked On Nicotine Checklist (HONC).** A measure of nicotine use and misuse. Duration: 2 minutes. (Difranza et al., 2002)
11. **Anxiety symptoms:** Generalized Anxiety Disorder Screener (GAD-7). The GAD-7 is a 7-item self-report measure assessing symptoms of generalized anxiety disorder. Respondents use a scale from 0 (‘not at all’) to 3 (‘nearly every day’) for each symptom. Duration: 1 minute. (Spitzer, Kroenke, Williams, & Löwe, 2006)
12. **Alcohol urge questionnaire (AUQ):** An 8-item measure of acute craving for alcohol. Duration: 2 minutes. (Bohn, Krahn, & Staehler, 1995)
13. **Mental health services:** We will ask if the participant is currently seeing or has seen in the past 90 days a therapist for a mental health problem and what condition. (screening)
14. **Medications and supplements:** A 2+ item measure on prescription and over the counter medications and supplements. Includes name of medication and reason for use. (**https://www.nimh.nih.gov/funding/clinical-research/clinical-research-toolbox/nimh-clinical-research-toolbox.shtml**)
15. **Treatment guess:** Do you think you received placebo or N-acetylcysteine? (standard treatment knowledge question)
16. **Military Service questions:** A 9-item measure of one’s military service. Duration: 2 minutes.

Interview:

- **SCID-5 AUD**: Semi-structured diagnostic interview for alcohol use disorder. (First, Williams, Karg, & Spitzer, 2015)
- **Physical exam:** completed by a physician who is an associate investigator on the study.

- **Pregnancy screen:** completed by a physician who is an associate investigator on the study. The Quidel QuickVue hCG Urine kit will be used.
- **COVID screen:** Participants will be screened for possible COVID symptoms and exposure.
- **Temperature screen:** Participants will be temperature checked with a non-contact thermometer.
- **Breathalyzer:** at each in-person appointment, we will assess BAC with a breathalyzer in compliance with the Department of Transportation (DOT)/National Highway Traffic Safety Administration (NHTSA).
- **Pill count and diary**: At each clinic visit, pill counts will be derived from returned pill bottles to determine intake and compare with the medication diaries that the participant is asked to fill out. (Lam et al., 2015)
- **Montgomery-Åsberg Depression Rating Scale (MADRS):** 10-item questionnaire assessing depression symptoms. (Williams & Kobak, 2008)
- **Alcohol Cue Reactivity (ACR):** a task in which the participant is exposed to stimuli associated with alcohol (Rohsenow et al., 2000). This task will be conducted with a virtual reality bar lab using the Oculus rift headset (https://www.oculus.com/rift-s/) and software from In Virtuo (http://invirtuo.com/en/). Please note that the cue reactivity software from In Virtuo is not directly displayed on their website, but is an adaptation of the PTSD bar scenario (http://invirtuo.com/en/software/software/).
- **Systematic Assessment for Treatment Emergent Effects (SAFTEE):**The SAFTEE is a systematic assessment of side effects for clinical trials. Participants are first asked about side effects in an open-ended way and then asked specifically about side effects that frequently occur. This measure takes approximately 5-10 minutes to complete. (Johnson, Ait-Daoud, & Roache, 2005)
    - **Note:** For phone sessions, the study staff will not administer the SAFTEE but rather ask the open-ended question, have you experienced any new or worsening side effects? Would you like to speak with the team physician prior to your appointment in one week?
- **Treatment questions:** We will ask if the participant is attending the Intensive Outpatient Program and seeing an individual provider at ATS. If no, we will ask why not to both. We will provide personalized recommendations to participants who answer no to both and their reason is anything other than that they completed their treatment at ATS because they improved.

Cognitive tasks:

Stop Signal Task - A task assessing impulse control and attention. Participants respond as quickly as they can to directional arrows by pressing computer keys. Some of the arrows are accompanied by an auditory tone indicating that the participant should not respond to that arrow. 9 minutes (Verbruggen et al. 2019; **https://www.millisecond.com/download/library/v5/stopsignaltask/stopsignaltask2019/stopsignaltask2019.manual**)

N-back task (2 and 3 back) - A task assessing working memory and information manipulation. Participants are shown a sequence of shapes and asked to respond to shapes that they've seen previously. 9 minutes (Jaeggi et al., 2010; **https://www.millisecond.com/download/library/v5/nback/singletasknback/singletasknback.manual**)

Trail Making Test (Trail a and Trail b) - A test assessing task-shifting. Participants draw lines connecting numbers and letters together in order. 3 minutes (Reitan, 1955; Tombaugh, 2004; **http://apps.usd.edu/coglab/schieber/psyc423/pdf/IowaTrailMaking.pdf**)

*Note, while training effects may occur on the cognitive tasks, this will be accounted for in the analyses. If there is an effect of NAC, it should lead to improvements greater than placebo. Recent estimates of the stop signal task and N-back task indicate fair to good reliability (~.5-.7) (Enkavi et al., 2019). However, a recent optimization of the Stop Signal Task is expected to improve reliability (Verbruggen et al., 2019). Likewise, a meta-analysis found good test-retest reliability (~.7) of the trail making test (Calamia et al., 2010).

Assessment	Screening: Phone Call	Baseline Visit (Wk 0)	In-person Visit 1 (W1)	Phone Call 1 (W2)	In-person Visit 2 (W3)	Phone Call 3 (W4)	In-person 3 (W5)	Phone Call 4 (W6)	Post-treatment visit (W7)
Physical Exam		x							
Informed Consent Form		x							
Inclusion /Exclusion Criteria	x								
Enrollment /Randomization		x							

Self-report									
Demographics		x							
ASSIST		x							
AUDIT		x							
APT		x	x		x		x		x
PACS		x	x		x		x		x
DDT		x	x		x		x		x
SIAS-6 and SPS-6		x	x		x		x		x
TLFB		x	x	x	x	x	x	x	x
E-cigarette questions		x							
HONC		x							
GAD-7		x	x		x		x		x
AUQ					x				
Mental health services		x							
Medications and supplements		x							
Treatment guess									x
Military service questions		x							
Interview									
SCID-5 AUD	x								
Breathalyzer		x	x		x		x		x
Temperature screen		x	x		x		x		x
COVID screen		x	x		x		x		x
Pill counts			x		x		x		x
MADRS		x	x		x		x		x
ACR					x				
SAFTEE			x		x		x		x
Have you experienced any new or worsening side effects?				x		x		x	
Treatment questions and personalized recommendations		x	x		x		x		x
Computer Tasks									
Stop Signal		x	x		x		x		x
N-back task		x	x		x		x		x
Trail Making task		x	x		x		x		x

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

○ Yes ◉ No

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-

group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

Independent samples t-tests will be used to evaluate for differences in dropout rate and total adverse events between study groups.

For our exploratory aims, we will assess the treatment effects on variables of interest using linear mixed models. Given the exploratory nature of analysis, we will report both false discovery rate corrected and nominally significant findings. See 11.6 for more detail on planned analyses.

11.2 Sample Size:

50

11.3 Total number of subjects requested (including records and specimens):

50

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

Arm 1: n-acetylcysteine. 25 participants randomly selected
Arm 2: placebo. 25 participants randomly selected

11.5 Please provide a justification for your sample size

Sample size justification. The primary aim of the present investigation is to establish feasibility, dropout rate, and the standard deviation of the outcome measures. The latter two are necessary to accurately estimate the sample size of the main trial. We are setting the pilot sample size in order to minimize the total sample size of the pilot and main trial together, recognizing that the pilot trial is part of a larger clinical development program. 40 participants (20 per arm) are needed to generate standard deviations (of the outcome measures) to be used in sample size calculation for the main trial assuming a main trial effect size in the small-to-medium range and power = .8.(Whitehead, Julious, Cooper, & Campbell, 2016) We will include an additional 10 participants to account for dropout, leading to a sample size of 50.

11.6 Data Analysis Plan: Complete description: Background, Objectives, Design, Step by Step how the project is going to be done, Data analysis plan:

Outcome analyses are exploratory as this is a pilot study. We will conduct these analyses to assess for a potential early efficacy signal as well as to inform future meta-analyses that aggregate our findings along with others to glean more definitive insights into the potential efficacy of NAC for an array of conditions.

Baseline values of continuous outcome variables will be tested for normality using the Shapiro-Wilk test (Razali & Wah, 2011). If normally distributed (< $\pm$ 2 skew and excess kurtosis), linear mixed-effects models (LMMs) will be used to evaluate the changes between baseline to post-treatment across the study groups taking into account within-subject associations over time. This approach is ideal for intention-to-treat analyses, because it uses all available data, and therefore all participants, including those with missing data, with no required imputations (Gueorguieva & Krystal, 2004). Furthermore, this approach reduces the variability of estimates by using all of the observations of the primary outcome measure, not just the baseline and treatment completion data points. In the event the data are not normally distributed, generalized linear mixed-effect models (GLMMs) will be applied to accommodate non-normal distributions in the data (Lo & Andrews, 2015). Fixed effects in the model will include the baseline outcome measure, treatment assignment, and a categorical time point. We will obtain adjusted, absolute between-group changes in outcome at each time point by including an interaction term between time point and treatment assignment (Espie et al., 2019). The model will also include a random participant-level effect. Sensitivity analyses will be conducted. Consistent with recommendations (e.g., Hallgren et al., 2016), items measured daily (i.e., drinks per drinking day, percent drinking days, percent days marijuana smoking, and cigarettes per day), will be aggregated into ~two-week averages corresponding to *time between each session* prior to statistical analysis.

Given the exploratory nature of the analyses, we will report both false discovery rate corrected (separated by primary, secondary, and tertiary aims) and nominally significant findings. We will run the primary analyses using all participants, and then re-run the analyses only using participants who had at least one follow-up session (i.e., "available cases"; Abraha et al. (2015)) and adherence of >80% as verified by the pill count and self-report (e.g., Gray et al. (2017)).

We will also assess marijuana and cigarette use if we have ample cases (N $\geq$ 10 in each group). Percent days marijuana smoking and cigarettes per day from baseline to the final session will also be assessed using LMMs (or GLMMs), but will be restricted to the subsets of individuals who report using marijuana and cigarettes, respectively, in the past month at the baseline session. For categorical smoking outcomes, chi square tests will assess for differences in rates of point prevalence abstinence (7 days at the end) and floating abstinence (any 7 day stretch). Missing cases will be assumed as having no abstinence on those days.

12.0 Participant Information

12.1 Subject Population:

Adult Military Healthcare Beneficiaries currently or formerly enrolled in an outpatient AUD treatment program at a MTF.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [x] 65-74
- [ ] 75+

18 - 74

12.3 Gender:

- [x] Male
- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [ ] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [x] Wounded Warriors
- [ ] Economically Disadvantaged Persons

- ☐ Educationally Disadvantaged Persons
- ☐ Physically Challenged (Physical challenges include visual and/or auditory impairment)
- ☐ Persons with Impaired Decisional Capacity
- ☐ Prisoners
- ☐ Pregnant Women, Fetuses, and Neonates
- ☐ Non-English Speakers
- ☐ International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

12.5 Inclusion Criteria:

Order Number	Criteria
1	≥ 18 years of age.
2	Meets DSM-V criteria for alcohol use disorder on the SCID-5
3	MHS Healthcare Beneficiary NOTE: While we are recruiting explicitly from the ATS patient population, we do not require that they are currently receiving treatment at ATS. For participants that are not currently in care we will provide them with resources to pursue psychotherapy while engaged in our study as outlined in the interview treatment questions and physical and mental health resource document.

12.6 Exclusion Criteria:

Order Number	Criteria
1	Lifetime clinical diagnosis of schizophrenia or bipolar disorder
2	Currently receiving medication for the treatment of alcohol use disorder including oral or injectable naltrexone (ReVia, Vivitrol), disulfiram (Antabuse), and acamprosate (Campral).
3	Pregnancy
4	Lack of English fluency sufficient to complete study measures.
5	Trying to get pregnant in the next 4 months.
6	Hospitalized because of alcohol use in the past 12 months.
7	History of seizures or delirium tremens.
8	History of liver disease
9	Diagnosis of a neurocognitive disorder (e.g., dementia, alzheimer's, intellectual disability).
10	Individuals who were never enrolled into ATS.

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

We will recruit for the study from the WRNMMC Addiction Treatment Services (ATS) clinic. During initial phone conversation, participants will complete a brief phone screen detailed in section 13.3.

13.2 Compensation for Participation:

Non-active duty/non-federal employee participants will be paid $265 total as follows:
$60 for baseline visit (1)
$40 per in-person visit (4)
$15 per phone call (3)

Participants who are active duty or federal employees are not eligible for payment. Participants will be informed on the consent form that their payment is taxable and that there is a chance that their payment could be withheld under certain circumstances. If they owe money to the government, their payment for study participation may be applied to that debt and not sent to them.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

Participants will complete a brief phone screen in which they will be asked the following eligibility criteria questions:

1. *Have you used any drugs other than marijuana in the past 30 days?*

   If yes: Which drugs?

2. *Have you ever had a seizure?*
3. *Have you ever had delirium tremens or DT?*
4. *Have you been to the hospital because of alcohol use in the past 12 months?*
5. *Have you ever been diagnosed with schizophrenia?*
6. *Have you ever been diagnosed with bipolar disorder?*
7. *Have you ever been diagnosed with a neurocognitive disorder such as dementia or Alzheimer's?*
8. *Have you even been diagnosed with an intellectual disability such as mental retardation? (NOTE: ADHD is ok)*
9. *Do you have any chronic medical conditions associated with alcohol use (such as liver disease)?*
10. *Are you currently receiving medication for the treatment of alcohol use disorder? If so, what medication are you taking?* [Exclude if taking oral or injectable naltrexone (ReVia, Vivitrol), disulfiram (Antabuse), and acamprosate (Campral)]
11. *Female only: Are you pregnant or trying to get pregnant sometime in the next 4 months?*
12. *How old are you?*

SCID-5 AUD module

If they meet eligibility criteria, they will be scheduled for their baseline visit. They will be told that they need to be abstinent from alcohol for at least 24 hours before their baseline appointment and that they will be breathalyzed to confirm a BAC of 0.

13.4 Consent Process: Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Participants will complete the consent process at the baseline visit in a private room at USU Building 53. Participants will be instructed to read the consent form and ask any questions before signing, then sign. A copy of the consent form with participant and research team signatures will be provided to participant following the consent process.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

◉ N/A
○ Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Participants may withdraw at any time by calling or emailing the study team. The study phone number and email are provided on the informed consent form. Participants will not have the opportunity to withdraw their data at any point in the study. Study withdrawal will not impact participant medical care or status in the military.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Side effects of NAC are uncommon and relatively minor. The most frequently reported side effects are nausea, vomiting, and diarrhea. They often occur at identical rates to placebo. Rarely and primarily with intravenous administration, anaphylactic reactions may occur and can consist of rash, pruritus, angioedema, bronchospasm, tachycardia, and blood pressure dysregulation. Finally, given the limited reports on NAC in pregnant and lactating women, it should not be used in this population in the context of research and thus this is an exclusion criteria.

Sources: 1) FDA approved acetylcysteine labels (**https://dailymed.nlm.nih.gov/dailymed/index.cfm**)
2) Minarini, A., Ferrari, S., Galletti, M., Giambalvo, N., Perrone, D., Rioli, G., & Galeazzi, G. M. (2017). N-acetylcysteine in the treatment of psychiatric disorders: current status and future prospects. *Expert opinion on drug metabolism & toxicology*, *13*(3), 279-292

Data collection may risk loss of privacy.

There is a risk of alcohol withdrawal.

There are legal risks if the participant enters the base intoxicated and/or the NSAB police are called.

There is a chance that participants could experience side effects such as nausea, motion sickness, eye strain, or seizures while completing the virtual reality-based assessment. Symptoms of virtual reality exposure can persist and become more apparent hours after use. These symptoms may put participants at an increased risk of injury when engaging in normal activities such as driving, operating machinery, or engaging in other demanding activities.

For military personnel, there is a risk that their command could be informed of their intoxication by the emergency department if the participant is transported there for alcohol withdrawal.

14.2
Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

As noted in the exclusionary criteria we will exclude participants who are using an FDA approved medication for AUD at the start of the study. There is no known risk to taking any of these medications concurrently with NAC, however, it is scientifically problematic to include participants taking these additional treatments. There are no other disqualifying concomitant medications.

Side effects will be managed as described in Section 16.1.

To minimize risks of side effects of virtual reality, participants will be screened prior to the virtual reality task to ensure they are safe to complete it. These procedures are outlined in the "NAC script" document. Participants who do not pass the screening will skip to the next procedure in the protocol.

To minimize risk of breach of confidentiality, records will be protected with data encryption technology, computer passwords, and locked cabinets. To protect against loss of PII we will use subject IDs on assessments.

14.3
Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e. g., child or spouse abuse

The information obtained will be stored electronically and in paper files in a secure location at USUHS Annex Building 53. Staff from the Institutional Review Board (IRB) at the Uniformed Services University and other government agencies as part of their duties, may look at these records to ensure privacy and security guidelines are followed. These duties include making sure that the research participants are protected.

Upon publication of research findings, deidentified data may be made open access consistent with an increasing number of journal policies. This enhances replicability, data aggregation, and potential scientific progress. For examples/further discussion, see:
https://journals.plos.org/plosone/s/data-availibility
https://www.frontiersin.org/articles/10.3389/fpubh.2017.00327/full

The paper consent forms will be kept in a locked filing cabinet in Dr. Gray's lab in a folder labeled with the participant ID for the duration of the study. These folders will only be accessible to approved study investigators and staff. At the end of the study, the consent forms will be

separated from the participant ID and maintained in a locked filing cabinet for three years, at which point they will be destroyed. The study email account will delete all outgoing messages to participants 3 years after completion of the study.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Individuals with AUD may see a reduction in alcohol use and co-occurring depression or anxiety by participating in the study, but there are no known benefits of NAC for AUD.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Consenting and assessment will take place in a private room to ensure patient confidentiality and ensure patient has privacy to ask and answer questions.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

If the participant endorses a high level of suicidal ideation on the MADRS, the study investigator (Dr. Gray) will follow up as needed to recommend necessary care (as specified in the attached SOP).

Although unlikely given participants will be actively in care, or recently in care at ATS, they will be informed of any unexpected findings in the study physical and told to follow up with their primary care provider (e.g., previously undiagnosed hypertension).

There is a chance that participants could face legal consequences for public intoxication if they present intoxicated at the security gate before their study visit. Additionally, if their blood alcohol content is between .01 and .049, the research team will ask them to stay at the study location for their safety until it is below that threshold. If they refuse to stay, the research team will reschedule their appointment and the participant can leave. Furthermore, if the participant's BAC is $\geq$.05, they may need to be transported to the WRNMMC emergency room to assess potentially dangerous alcohol withdrawal. If they refuse to go to the emergency department, the research team may need to contact the local police to inform them of the situation.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- (●) DSMP
- ( ) DSMB
- ( ) Both
- ( ) Not Applicable

A DSMP should describe the plan to monitor the data to verify that the data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored, and the frequency of monitoring. It should also include the plan to ensure the safety of subjects

Data Safety Monitoring Plan (DSMP)

Study Title:

A pilot study of N-acetylcysteine for alcohol use disorder

Type of Research Data or Events to be Monitored:

We will monitor the collection, confidentiality, and security of all data collected in this study.

This monitoring plan will also maximize participant safety via the monitoring and reporting of adverse events and unanticipated problems as detailed in Section 16.0 Reportable Events and copy and pasted below for convenience.

Methods and Frequency of Analysis:

Data acquisition will be ensured during each session using checklist "flowsheets" (attached to the protocol). The PI will review the full collection of data at least monthly. All data will be stored in locked filing cabinets, secure USU computers, and deidentified data on secure google drive folders.

A study physician will conduct physical exams prior to enrollment and will monitor participants for side effects. Participants will be asked about adverse events weekly by the study physician. Participants may withdraw from the study at any time by contacting the research team, as stated in the consent form. The principal investigator may terminate any individuals' participation in the study at any time if he determines this to be in their best interest, if they are unable to comply with the procedures required, or if they no longer meet eligibility criteria.

Person(s) Responsible for Data Monitoring:

The data will be monitored by the principal investigator, Dr. Joshua Gray, and the research team: Steven Dufour, Matthew Thompson, Ashton Rouska, Lauren Schultz, and Mikela Murphy.

Dr. Joshua Gray will be responsible for submitting reports of unanticipated problems, serious adverse events, protocol deviations to the IRB and FDA as indicated.

Incidental or Unexpected Findings will be handled as detailed in 14.6

Reportable Events and plan to respond is detailed in Section 16.0

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Expected Adverse Events (EAEs)
The primary EAEs for the study will be potential medication side effects.
Side effects are uncommon and relatively minor. The most frequently reported side effects are nausea, vomiting, and diarrhea. They often occur at identical rates to placebo. Rarely and primarily with intravenous administration, anaphylactic reactions may occur and can consist of rash, pruritus, angioedema, bronchospasm, tachycardia, and blood pressure dysregulation. Finally, given the limited reports on NAC in pregnant and lactating women, it should not be used in this population in the context of research and thus this is an exclusion criteria.

Sources: 1) FDA approved acetylcysteine labels (**https://dailymed.nlm.nih.gov/dailymed/index.cfm**)
2) Minarini, A., Ferrari, S., Galletti, M., Giambalvo, N., Perrone, D., Rioli, G., & Galeazzi, G. M. (2017). N-acetylcysteine in the treatment of psychiatric disorders: current status and future prospects. *Expert opinion on drug metabolism & toxicology*, *13*(3), 279-292.

To assess them, the study physician will use the Systematic Assessment for Treatment Emergent Events (SAFTEE) interview at each in-person appointment. This includes asking about common symptom indicators as well as an "other" option to record other side effects:
NAUSEA
Minimal: Single occurrence, lasting less than 2 hours; no change in eating habits
Mild: Multiple occurrences or duration longer than 2 hours; no change in eating habits
Moderate: Intake significantly less than minimum daily requirement, but able to eat
Severe: No significant nutritional intake

VOMITING
Minimal: Stomach contractions, retching, or heartburn without emesis
Mild: 1 episode in any 24-hour period
Moderate: 2-5 episodes in 24 hours or 1 episode per day on 5 or fewer days
Severe: 6-10 episodes in 24 hours or more than 1 episode on more than 5 days

DIARRHEA
Minimal: Loose but not watery stools, without cramping or incontinence
Mild: Diarrhea without cramping or incontinence
Moderate: Diarrhea with cramping, no incontinence
Severe: Diarrhea with incontinence and cramping

ABDOMINAL PAIN
Minimal: Single occurrence of abdominal pain that is not distressing and does not limit activities
Mild: Multiple occurrences of abdominal pain that is not distressing and does not limit activities *Moderate:* Single or multiple occurrences of abdominal pain that causes distress but does not limit activities
Severe: Abdominal pain or cramping of sufficient severity to limit activities

CHANGE IN APPETITE
Minimal: Hunger increased or decreased without change in food intake or weight
Mild: Hunger increased or decreased, with change in food intake and pre-study weight stable or less than 5% reduction
Moderate: Hunger increased or decreased; change in food intake and 5%-10% weight loss or gain present without intention to diet or gain weight
Severe: Hunger increased or decreased; weight loss or gain of more than 10% of pre-study weight without intention to diet or gain weight

HEADACHE
Minimal: Single occurrence of headache that is not distressing and does not limit activities
Mild: Multiple occurrences of headache that is not distressing and does not limit activities *Moderate:* Single or multiple occurrences of headache that causes distress but does not limit activities
Severe: Headache with pain of sufficient severity to limit activities

DIZZINESS

Minimal: Occasional transient subjective dizziness, lasting less than 1 minute per occurrence; no limitation of function and no objective findings
Mild: Subjective dizziness lasting greater than 1 minute; no objective findings and no impairment of function
Moderate: Dizziness with impairment of function or limitation of activities; nystagmus or increased body sway noted on exam
Severe: Dizziness with impairment of function, falling, or syncope

FATIGUE
Minimal: Subjective fatigue without increased need for rest; able to perform all activities of daily living (ADLs)
Mild: Subjective fatigue with increased need for rest; able to perform all ADLs
Moderate: Subjective fatigue with increased need for rest; able to perform ADLs only with effort *S evere:* Unable to perform ADLs; able to meet basic needs only with assistance

NERVOUSNESS/ANXIETY
Minimal: Occasional nervousness/anxiety that does not cause distress or limit activities
Mild: Occasional nervousness/anxiety that is distressing but tolerable and does not limit activities
Moderate: Occasional or persistent nervousness/anxiety that is distressing but tolerable and limits activities
Severe: One or more panic attacks or persistent nervousness/anxiety that is intolerable

INSOMNIA
Minimal: Sleep that is not restful, but without change in amount or pattern of sleep
Mild: More than between 1 and 3 occasions of unexplained difficulty falling asleep or of increased nocturnal awakenings, but without change in amount of sleep
Moderate: More than 3 occasions of unexplained difficulty falling asleep and nocturnal awakenings with significant reduction in sleep, but without daytime impairment of function *Sever e:* More than 3 occasions of unexplained difficulty falling asleep and nocturnal awakenings with significant reduction in sleep, with daytime impairment of function

SOMNOLENCE
Minimal: Occasional subjective tiredness but without change in daily activities
Mild: Persistent subjective tiredness, but without change in daily activities
Moderate: Persistent subjective tiredness; requiring resting or napping less than 2 hours during the day
Severe: Persistent tiredness that significantly limits daily activities, requiring napping or resting more than 2 hours daily; falling asleep during work, school, or other activities

DEPRESSION
Minimal: Occasional depressed mood that does not cause distress or limit activities
Mild: Occasional depressed mood that is distressing but tolerable, and does not limit activities *Mo derate:* Occasional or persistent depressed mood that is distressing but tolerable, and is associated with a change in activities
Severe: Suicidal ideation or persistent depression that is intolerable and is associated with a change in activities

ITCHING
Minimal: Localized itching without need to scratch
Mild: Localized itching with scratching
Moderate: Generalized itching that is tolerable and does not interfere with sleep or activities *Seve re:* Generalized itching that is intolerable and interferes with sleep and/or activities

SKIN RASH
Minimal: Localized erythema or localized macular/ papular eruption, lasting less than 48 hours and without symptoms
Mild: Localized erythema or localized macular/ papular eruption, lasting greater than 48 hours and without symptoms
Moderate: Erythema or macular/papular eruption with pruritus or other associated symptoms involving more than one site on the body
Severe: Generalized (most of body affected) symptomatic macular, papular or utricarial or atypical eruption with or without mucous membrane involvement and with or without exfoliative dermatitis or ulcerating dermatitis

CHANGE IN LIBIDO
Minimal: Occasional increase or decrease in libido that does not engender distress or concern to the subject; no change in sexual activity or performance
Mild: More persistent libido increase or decrease that does not engender distress or concern to the subject; no change in sexual activity or performance

Moderate: More persistent libido increase or decrease that does engender distress or concern to the subject; changes in sexual activity or performance reported
Severe: Significant increase or total lack of interest in sex that is distressing or of concern to the subject; associated with changes in sexual activity or performance

MISSED MENSES
Minimal: Single occurrence of delayed menses (one cycle) that are otherwise regular
Mild: Single occurrence of absent menses (one cycle) that are otherwise regular
Moderate: Multiple occurrences of delayed or absent menses
Severe: Total amenorrhea

Reporting EAEs
All EAEs will be reported every 12 months to the IRB.

Moderate-Severe EAEs that are thought to be potentially attributable to the medication will be reported within 48 hours to the IRB. Additionally, the participant will be reminded of their choice to stop the medication and withdraw from the study at any time. The study physician will use medical judgement for requiring the participant to discontinue the medication and participation. Unblinding will occur in the event of a severe EAE that is thought to be related to medication or at the discretion of the study physician.

Serious Adverse Events (SAEs)
SAEs are AEs that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting of Serious Adverse Events
SAEs will be reported by the PI to the IRB within 48 hours of learning of the event. SAEs will be reported regardless of whether they are attributable to participation in the study (e.g,. suicide).

Unexpected Adverse Events (UAEs) and Unanticipated Problems
UAEs are AEs that are reported by the participants that are beyond the typical side effects of NAC. The study physician will provide guidance to the participant on whether they should discontinue the medication and study.

Unanticipated problems involving risks to participants will also be reported to the IRB. These events are a broader category of events than AE and can include breach of confidentiality, misplaced data, or other unexpected distress attributable to study participation.

Reporting UAEs and Unanticipated Problems
UAEs and unanticipated problems will be reported to the IRB within 48 hours of the PIs knowledge.

Reporting to the FDA
Dr. Joshua Gray will be responsible for submitting reports of unexpected fatal or life-threatening suspected adverse reactions to the appropriate FDA IND Division no later than 7 calendar days after initial receipt of the information using the MedWatch Form 3500a.
Dr. Joshua Gray will also be responsible for reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the appropriate FDA IND Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a.

Clinical Follow-up Plan
All moderate AEs will be followed until either resolution or mild and deemed stable by a treating provider. Any AE that Dr. Livezy or other medical professionals at the clinical research unit deem to require further management will be referred to the participant's primary care manager. For SAEs that warrant emergency services or possible admission, participants will be referred to the WRNMMC ED for further management.

Pausing and Stopping Rules
We will pause the protocol if we have 1 SAE deemed potentially related to the study participation. Upon further investigation of the cause of the SAEs, a decision will be made to resume the protocol or stop the study.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☑ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

☐ Are drug(s) in this research being used in accordance to the approved labeling?
☑ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** n-acetylcysteine **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	150689

Trade Drug Name:	n-acetylcysteine
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Medisca
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved	Yes

drug	
Is an IND necessary	Yes
IND Number	150689
Who holds the IND:	PI holds the IND
IND details:	30 day review from May 13 - June 12 2020. Matthew Sullivan, MS RAC (matthew.sullivan@fda.hhs.gov) from the Center for Drug Evaluation and Research (CDER). See attached email correspondence. Requested: "Provide stability data for the drug product and placebo; typically at least 30 days is provided. Update the IND as additional data becomes available." We will ask Medisca for stability data for each batch of NAC that is ordered. We will email this information to Matthew Sullivan.
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	1500mg
Frequency:	BID
Route of administration:	Oral
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	The source is Medisca which is Certified to the ISO 9001: 2015 standard and the compound is USP grade.
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	Compounding will be conducted by the WRNMMC investigative pharmacy. 500mg of NAC will be placed in each pill. Matching placebo pills will be prepared. Each gelatin size 0 capsule contains 500mg of acetylcysteine, USP powder or 550mg of lactose anhydrous, NF powder. For the placebo, the maximum capacity of size 0 capsule is about 559mg of lactose anhydrous, NF and all they have to do is pack it to capacity, no need to weigh. They capsules are from Letco Medical and the NDC for the capsule is 62991-4010-05 The pharmacy will handle gender stratified randomization. Participants will pick up the medication from the Investigational Pharmacy at the end of appointments 0, 1, and 3. Participants will be escorted there if they have never been there before. If a participant misses an appointment, they will also be asked to pick up the medication at week 5.
Indication(s) under Investigation:	Alcohol use disorder, depression, anxiety.
Where will the drug be stored	The pharmacy where it will be locked and secure.
Drug Storage Restrictions (including temperature, etc.):	The locked area will be maintained under controlled temperature conditions at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).

Administration Instructions:	Take 3 tablet/capsule by mouth twice a day. Please try to take it at the same times each day. Volunteer's Storage Conditions: Keep in a dry area away from children.
Possible Untoward Effects, Their Symptoms & Treatment:	See section 14.1 and 16.1
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	Consult with study physician. Consider ceasing use.
Contraindications and Interactions, If Known:	See section 14.1 and 16.1
Investigators Authorized to Prescribe:	LTC Jeffrey Livezey, MD MSc COL David Saunders, MD MPH

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

Dr. Joshua Gray will be responsible for submitting reports of unexpected fatal or life-threatening suspected adverse reactions to the appropriate FDA IND Division no later than 7 calendar days after initial receipt of the information using the MedWatch Form 3500a. Dr. Joshua Gray will be responsible for reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to the appropriate FDA IND Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a.

18.5 Sponsor (organization/institution/company):

☐ N/A

If applicable, provide sponsor contact information:

Dr. Joshua Gray
joshua.gray@usuhs.edu

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ○ Registration is not required
- ○ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:

NAC = n-acetylcysteine
AUD = alcohol use disorder
USU = Uniformed Services University
FDA = Food and Drug Administration
PTSD = posttraumatic stress disorder
TBI = traumatic brain injury
RA = research assistant
BAC = blood alcohol content
WRNMMC = Walter Reed National Military Medical Center
LMMs = linear mixed models
GLMMs = generalized linear mixed models
AA = alcoholics anonymous
PII = personally identifiable information
SOP = standard operating procedure
DSMP = data safety monitoring plan
AEs = adverse events
EAEs = expected adverse events
SAEs = serious adverse events
UAEs = unexpected adverse events
ATS = Addiction Treatment Services

NAC Informed Consent for Breathalyzer

Title: A pilot study of n-acetylcysteine for alcohol use disorder
Principal Investigator: Joshua C. Gray, PhD

At the beginning of each in-person study appointment, you will be given a breathalyzer test to ensure that your blood alcohol content (BAC) is 0, meaning that you have not come to the study appointment intoxicated. A member of the study team will instruct you to blow into the breathalyzer. If your BAC is 0, you will proceed with the study procedures. If your BAC is above 0, the study team member will have you wait a few minutes and blow into the breathalyzer again. If your BAC is between .01 and .049, we will ask you to stay at the study location for your safety until it is below that threshold. If you refuse to wait, we will reschedule your study appointment and you can leave. Furthermore, if your BAC is $\geq$.05, **you will be transported to the WRNMMC Emergency Department to assess potentially dangerous alcohol withdrawal. If you refuse, we may need to contact the local police to inform them of the situation.** For military personnel, there is a risk that your command could be informed by the Emergency Department of your intoxication. There is a potential for increased medical cost if you are brought to the ER and have lost your DoD healthcare beneficiary status since the start of the study.

IF THERE IS ANY PORTION OF THIS DOCUMENT THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING.

SIGNATURE OF PARTICIPANT

By signing below, I agree that I have been provided time to read the information describing the research study in the breathalyzer consent form. The content and meaning of this information has been explained to me. I have been provided with the opportunity to ask questions. I voluntarily consent to participate in this portion of the study.

By signing this form, I have not given up any of my legal rights as a research participant.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT
(Can only be signed by an investigator or staff approved to administer consent)

_____
Printed Name of Administering Individual

_____ _____

Signature of Administering Individual Date

Uniformed Services University
CONSENT TO PARTICIPATE IN RESEARCH
Title: A pilot study of N-acetylcysteine for alcohol use disorder
Principal Investigator*:* Joshua C. Gray, PhD

You may be eligible to take part in this research study. This form gives you important information about the study.

Please take time to carefully review this information. You should talk to the researchers about the research study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or your personal physician) about your potential participation in this research study. You do not have to take part in this study. Participation is voluntary. You may also leave the research study at any time without penalization.

1. KEY INFORMATION:

Your consent is being sought for this research study. This proposed study aims to assess the effects of N-acetylcysteine (NAC) on alcohol use disorder. Alcohol use disorder affects over 15 million adults, yet many of those affected do not significantly benefit from currently approved pharmacotherapies for alcohol use disorder. NAC is one promising pharmacotherapy for alcohol use disorder that has minimal side effects.

If you choose to participate, you will be randomized to take either placebo or 3000mg of NAC daily for 7 weeks. You will be asked to attend 5 in-person study sessions (this includes the session today). Today's session will last approximately 3 hours. The other in-person sessions will last approximately 2 hours each. Additionally, you will be asked to complete 3 phone calls every other week, lasting 30 minutes each. You will receive a routine physical examination conducted by a physician to ensure you are eligible to participate and you will complete psychological and cognitive testing. You must have a blood alcohol content of 0 at each visit to participate which will be confirmed by a breathalyzer. **This is an experiment testing a medication for alcohol use disorder, thus we do not know if it is helpful.** If you are not active duty or a federal employee, you will be paid up to $265. However, please note that you will not receive payment on the day of your session and your payments can take **up to 10 weeks** to process. Risks of participating in this study include side effects of NAC; nausea, vomiting, and diarrhea. Alternative treatments include psychotherapy, inpatient treatment, outpatient treatment, and FDA-approved medications for alcohol use disorder.

If you decide to take part in this research study, you will be asked to sign this document. Before you sign this document, be sure you understand what the research study is about in all sections of the consent form, including the risks and possible benefits to you.

Please tell the researchers if you are taking part in another research study.

2. WHAT IS THE PURPOSE AND DURATION OF THIS RESEARCH AND WHO WILL TAKE PART?

You are being asked to take part in this research study because you have alcohol use disorder, are open to reducing your drinking, and are a current or former patient of Addiction Treatment Services (ATS) at Walter Reed National Military Medical Center (WRNMMC). The purpose of this research study is to learn about the potential efficacy of an investigational drug, NAC, for the treatment of alcohol use disorder. The duration of participation per visit is 3 hours for the baseline session, between 2 and 2.5 hours for the remaining in-person sessions, and 30 minutes per phone session.

Study sessions during weeks 0 (i.e., today), 1, 3, 5, and 7 will take place in person at USU buildings 17 and 53. Study sessions during weeks 2, 4, and 6 will take place over the phone.

There will be about 50 people taking part in the study at USU, over a period of approximately 2-4 years.

This research study involves an investigational drug called N-acetylcysteine (NAC). This means that is has not yet been approved or cleared by the Food & Drug Administration (FDA) for treating alcohol use disorder. However, the FDA has not objected to its use in this research study to learn more about its safety and/or effectiveness.

3. SCREENING PROCESS TO QUALIFY FOR PARTICIPATION IN THIS STUDY

Before you can take part in this study, you will need to have some tests and provide some information so that the Investigator can confirm that you qualify for the study. This is called the "Screening Process." You will undergo a physical examination completed by a physician, who is an associate investigator on the study. You will not be eligible to participate if the physical examination reveals a serious medical condition that contraindicates your participation or if you are pregnant as verified by a pregnancy test. Further, if you are pregnant, you will be instructed to contact your primary care provider to confirm the results and discuss the risks of alcohol use during pregnancy. Additionally, you must be between the ages of 18 and 74 to participate.

4. WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH?

You will be randomly assigned to receive NAC or placebo. You will be asked to take the medication twice daily for 7 weeks. You will be assessed weekly on your drinking habits, craving, depression and anxiety symptoms, adverse events, and cognitive functioning. Study sessions during weeks 0 (i.e., today), 1, 3, 5, and 7 will take place in person at USU buildings 17 and 53. During weeks 0, 1, and 3, you will be asked to pick up your study medication at the Investigational Pharmacy, located in building 9. Study sessions during weeks 2, 4, and 6 will take place over the phone.

During the phone sessions you will be asked questions regarding your alcohol use and any potential side effects of the study medication. During the in-person sessions you will first be assessed for alcohol intoxication and adverse side effects. Then you will be asked to answer several questionnaires related to your consistency of taking the medication and psychological health. Finally, you will also be asked to complete several cognitive tasks and participate in an alcohol cue-reactivity task, where you are exposed to stimuli associated with alcohol in a virtual reality bar lab. During the week 3 in-person session, you will be asked to complete a virtual reality-based assessment. The virtual reality-based assessment will involve watching virtual scenes while we measure your responses, as described below.

The virtual reality-based assessment will measure your alcohol cue reactivity by exposing you to situations with the use of virtual reality. Prior to the assessment, you will be asked several screening questions to assess whether it will be safe for you to complete the virtual reality-based assessment. For the assessment, you will be asked to wear a head-mounted display, which is like a hat with mini-television screens in front of your eyes. A member of the research team will help you and will be present at all times. Scenario settings include bar scenes and other scenes related to drinking alcohol.

You will be randomly assigned to one of 2 groups. Randomization is a process like flipping a coin and means you will have a chance of being assigned to either of the groups. One of the groups will receive NAC and the other group will receive the placebo.

You will have a one in two chance of being in the placebo group. A placebo is an inactive, harmless substance, like a sugar pill, that looks like the research study medication but contains no medication.

This research study is a double-blind study, which means that neither you nor the research team will know whether you are receiving the research study medication or a placebo. In the event of an emergency, there is a way to find out which one you are receiving. At the end of the study, you will not learn whether you received placebo or NAC due to possible issues with unblinding the study team.

5. WHAT ARE THE RISKS OR DISCOMFORTS FROM BEING IN THIS RESEARCH?

If you choose to take part in this study, there is a risk of someone getting access to the information researchers have stored about you. We have detailed precautionary measures we are taking in Section 15.

There is a chance that you could face legal consequences for public intoxication if you present intoxicated at the security gate before your study visit. Additionally, at the beginning of each session you will be administered a breathalyzer to check your blood alcohol content (BAC). If your BAC is between .01 and .049, we will ask you to stay at the study location for your safety until it is below that threshold. If you refuse to wait, we will reschedule your study appointment and you can leave. Furthermore, if your BAC is ≥.05, you will be transported to the WRNMMC Emergency Department to assess potentially dangerous alcohol withdrawal. If you refuse, we may need to contact the local police to inform them of the situation. For military personnel, there is a risk that your command could be informed by the Emergency Department of your intoxication. There is a potential for increased medical cost if you are brought to the ER and have lost your DoD healthcare beneficiary status since the start of the study.

There is a chance that your payment could be withheld under certain circumstances. If you owe money to the government, your payment for study participation may be applied to that debt and not sent to you.

We may also break confidentiality to inform ATS of matters that they were previously unaware of that may impact your safety (e.g., previously undisclosed intent to attempt suicide).

The safety of this drug in humans has been tested in prior research studies and it is FDA approved for the treatment of acetaminophen poisoning. However, please note that this drug is not approved for alcohol use disorder. This research study will test the preliminary effectiveness of this drug taken by mouth as well as the tolerability in a population of adults with alcohol use disorder.

Side effects are uncommon and relatively minor. The most frequently reported side effects are nausea, vomiting, and diarrhea. Rarely and primarily with intravenous administration, anaphylactic reactions may occur and can consist of rash, itchiness, swelling, difficulty breathing, rapid heart rate and high or low blood pressure. Finally, given the limited reports on NAC in pregnant and lactating women, it should not be used in this population in the context of research. The use of birth control is recommended to avoid pregnancy.

Sources: 1) FDA approved acetylcysteine labels (https://dailymed.nlm.nih.gov/dailymed/index.cfm)
2) Minarini, A., Ferrari, S., Galletti, M., Giambalvo, N., Perrone, D., Rioli, G., & Galeazzi, G. M. (2017). N-acetylcysteine in the treatment of psychiatric disorders: current status and future prospects. *Expert opinion on drug metabolism & toxicology*, *13*(3), 279-292.

Although efforts are made to protect your research study records, there is always a risk that someone could get access to the medical information contained in your research records or other information researchers have stored about you.

It is not known whether NAC can cause birth defects or other problems in an unborn child. If you become pregnant or feel you might be pregnant, contact your personal physician and the principal investigator of this study listed in the Contact Information section at the end of this document.

There is a chance that you could experience side effects such as nausea, motion sickness, eye strain, or seizures while completing the virtual reality-based assessment. Symptoms of virtual reality exposure can persist and become more apparent hours after use. These symptoms may put you at an increased risk of injury when engaging in normal activities such as driving, operating machinery, or engaging in other demanding activities. Because virtual reality is new, there may be other risks that are currently unknown.

DoD-affiliated personnel (military or federal civilian employees) with any concerns about study risks and fitness for duty should seek command or Component guidance before participating.

There may also be other risks of taking part in this study that we do not yet know about.

6. WHAT ARE THE POSSIBLE BENEFITS FROM THIS RESEARCH?:

The possible benefits to you as a research participant in this research study are that NAC may help with alcohol use disorder symptoms and co-occurring depression or anxiety. However, there is no guarantee that you will benefit from being in this research.

7. WHAT ARE THE ALTERNATIVES TO TAKING PART IN THIS RESEARCH?

There may be other options for treating alcohol use disorder. Alternative treatments and/or procedures that may be available to you include: psychotherapy, inpatient treatment, outpatient treatment, and FDA-approved medications for alcohol use disorder. You should talk with your personal physician (if applicable) about these options.

Choosing not to take part in this research study is also an option. There may be other research studies involving experimental treatments that could be helpful to your condition.

8. IS THERE COMPENSATION FOR YOUR PARTICIPATION IN THIS RESEARCH?

Non-active duty/non-federal employees will receive a maximum compensation of $265 for completing this study. Payment will be provided in a form of a check or ACH payment after the study visit is completed. We will collect your social security number, name, address, and banking information on a form in order to complete your payment. You will be given the option to either a) complete this form at the end of your appointment; b) complete this form electronically and send to us by email; or c) print and fill out this form and send to us by mail. It may take up to 10 weeks to clear your payment. We understand this is inconvenient, but this is the only way we are able to pay you. Please be aware that this payment is taxable and may be withheld if you owe money to the government. The following payment schedule will be used for non-active duty/non-federal employees:
Baseline visit (1): $60
In-person visits (4): $40 each.
Phone Calls (3): $15 each.

Even if you are an off-duty federal employee you may not be compensated because this study is funded by a federal source (DoD).

9. ARE THERE COSTS FOR PARTICIPATING IN THIS RESEARCH?

Yes, there are costs to you for taking part in this research study. These include the costs to travel to the study sessions.

10. PRINCIPAL INVESTIGATOR (the person(s) responsible for the scientific and technical direction of the study):

Dr. Joshua C. Gray
Assistant Professor
Department of Medical and Clinical Psychology
Uniformed Services University
nacstudy@usuhs.edu
(301) 941-7908

11. STUDY SPONSOR (the organizations or persons who oversee the study and are responsible for analyzing the study data):

USU is the sponsoring organization.

As the sponsor of this research, the Department of Defense may have access to your research data in accordance with DoDI 3216.02.

12. SOURCE OF FUNDING:
This study is funded by USU start-up funding and also potentially from other grants which are currently being reviewed.

13. LOCATION OF THE RESEARCH:
Uniformed Services University, buildings 17 and 53.

14. DISCLOSURE OF FINANCIAL INTERESTS AND OTHER PERSONAL ARRANGEMENTS:
No members of the research team have financial interests to disclose.

15. WHO WILL SEE MY INFORMATION (PRIVACY) AND HOW WILL IT BE PROTECTED (CONFIDENTIALITY)?
Records of your participation in this research study may only be disclosed in accordance with state and federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. DD Form 2005, Privacy Act Statement - Military Health Records, contains the Privacy Act Statement for the records. A copy of DD Form 2005 can be given to you upon request, or you can read on-line at: https://www.esd.whs.mil/Portals/54/Documents/DD/forms/dd/dd2005.pdf

The research team will keep your research records. These records may be looked at by staff from the Uniformed Services University, the Institutional Review Board (IRB), and the DoD Higher Level Review as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed.

Procedures to protect the confidentiality of the data in this study include but are not limited to records will be protected with data encryption technology, computer passwords, and locked cabinets. Participants will be assigned a subject ID to prevent the release of personally identifying information.

Researchers will make every effort to protect your privacy and confidentiality; however, there are risks of breach of information security and information loss.

If applicable, 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 results. You can search this web site at any time.

We may share your data with outside researchers, collaborators, or as a part of the publication of the research findings, but only after all information that can identify you has been removed. This data may be used for a variety of research purposes that we may not be able to specify at this time. Complete confidentiality cannot be promised for military personnel, because information regarding your health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

The USU study team will have access to your records and agree to safeguard your protected health information by using and disclosing it only as permitted by you in this consent or as directed by state and federal law.

Information gained from your participation in this research study may be published in literature, discussed for educational purposes, and used generally to further science. You will not be personally identified when your information is shared in these ways; all information will be de-identified.

For this research study, a Department of Health and Human Services (DHHS) Certificate of Confidentiality is in place to protect your privacy such as your name or other identifying information from being disclosed in any civil, criminal, administrative, legislative or other proceedings, whether at the federal, state or local level. The Certificate cannot be used to resist a demand for information from personnel of the U.S. Government that is used for auditing or evaluation of Federally-funded projects or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA). Further, the researcher is not prevented from disclosure for reporting matters such as family abuse, sexual assault, reportable communicable diseases, a participant's threatened violence to self or others, or as military regulations may require. You should understand that the Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

16. LONG TERM USE OF DATA

The investigator has requested to save selected data collected from your participation in this research study for possible use in future research. Identifiers will be removed, and de-identified information may be used or shared for future research. If you do not want your deidentified data to be used long term, you should not consent to participate in this study.

Any future research using your retained data will require a research protocol for the proposed study approved by an Institutional Review Board (IRB) (a committee responsible for protecting research participants) or other authorized official responsible for protecting human subjects of research. The data protections for privacy and confidentiality described in this consent form will apply to any future use of your stored data.

17. USE OF INFORMATION AND SPECIMENS

During this research study, you could be asked to provide the following types of samples (biological specimens): urine for a pregnancy test. Identifiers will be removed from all biospecimens given in this study and they will not be used or shared.

The information that we obtain from you for this study might be used for future studies. We may remove anything that might identify you from the information. If we do so, that information may then be used for future research studies or given to another investigator without getting additional permission from you.

Upon publication of research findings, deidentified data may be made publicly available to anyone consistent with an increasing number of journal policies. This enhances replicability, data aggregation, and potential scientific progress. For examples/further discussion, see:
https://journals.plos.org/plosone/s/data-availibility
https://www.frontiersin.org/articles/10.3389/fpubh.2017.00327/full

18. INCIDENTAL FINDINGS

There is a possibility that during your physical exam we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by phone. In the case of a potential serious emergency, the researcher will inform you right away.

We will also give information about this incidental finding to your primary doctor. We will request your primary doctor's contact information in order to inform them.

- An incidental finding may cause you to feel anxious
- Since an incidental finding will be part of your medical record, you could face greater difficulty in getting health or life insurance

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility. If you are a DoD beneficiary, you will have access to care through standard Military Health System and TRICARE procedures.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding.

If we determine that you are in an acute psychological emergency, the principal investigator, Dr. Gray, will speak with you to confirm the emergency and have you escorted to the WRNMMC Emergency Department.

19. VOLUNTARY PARTICIPATION

The decision to take part in this research study is completely voluntary on your part which means you do not have to take part if you do not want to. You may also leave the research study at any time. If you choose not to take part in this research study or if you leave the study before it is finished, there will be no penalty or loss of benefits to which you are otherwise entitled.

You will be informed if significant new findings develop during the course of this research study that may relate to your decision to continue participation.

20. WHAT HAPPENS IF I WITHDRAW FROM THIS RESEARCH?

Should you choose to withdraw, you must email the research team at nacstudy@usuhs.edu or call (301) 941-7908. There are no known risks of withdrawing from the treatment medication, however, we ask that you please contact us prior to withdrawing from the study or medication. If you decide to no longer participate in this research study, the researcher will keep your

deidentified data that was part of this research study. You may withdraw your consent at any time and stop participating in this research study without affecting your eligibility for care, status in the military, or any other benefits to which you are entitled.

If you are receiving treatment as part of this research study, you will no longer be eligible for such research-related treatment. Contact your personal physician to discuss medical treatment for your condition.

The principal investigator of this research study may terminate your participation in this research study at any time if he determines this to be in your best interest, if you are unable to comply with the procedures required, or if you no longer meet eligibility criteria.

21. WHAT HAPPENS IF YOU ARE INJURED AS A RESULT OF THIS RESEARCH?

If you think that you have a research-related injury, notify your Principal Investigator immediately using the contact information in the section below.

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree), you are authorized space-available medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at DoD hospitals or DoD clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are authorized space-available medical care for your injury at a DoD hospital or an DoD clinic; medical care charges for care at a DoD hospital or a DoD clinic will be waived for your research-related injury. If you obtain care for research-related injuries outside of a DoD or DoD hospital or clinic, you will not be reimbursed for those medical expenses.

For DoD healthcare beneficiaries and non-DoD healthcare beneficiaries: Transportation to and from hospitals or clinics will not be provided or paid for by DoD. Unless you are covered by TRICARE, no DoD reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights.

22. CONTACT INFORMATION:

Principal Investigator (PI)

The Principal Investigator or a member of the research staff will be available to answer any questions throughout this study.

Principal Investigator: Dr. Joshua C. Gray
Phone: (301) 941-7908
Mailing Address:
Uniformed Services University
Department of Medical and Clinical Psychology
4301 Jones Bridge Rd
Bethesda, MD 20814

Uniformed Services University Human Research Protection Program (HRPP) Office
The Human Research Protection Program Office Point of Contact and/or Human Protections Administrator (HPA) will be available to answer questions or discuss concerns you may have about this research study.

Human Protections Administrator/HRPP POC: Petrice Longenecker, PhD, CIP
Phone: 301-295-0819

Institutional Review Board (IRB) Office
If you have any questions about your rights as a research participant or if you have concerns or complaints about the research study, please contact the IRB Office at: (301) 319-4730
Uniformed Services University
Human Research Protections Program Office
4301 Jones Bridge Rd
Bethesda, MD 20814

IF THERE IS ANY PORTION OF THIS DOCUMENT THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. YOU MAY CONSULT WITH YOUR PERSONAL PHYSICIAN OR LEGAL ADVISOR, IF YOU WISH.

A signed and dated copy of this document will be given to you.

SIGNATURE OF PARTICIPANT

By signing below, I agree that I have been provided time to read the information describing the research study in the consent form. The content and meaning of this information has been explained to me. I have been provided with the opportunity to ask questions. I voluntarily consent to participate in this study.

By signing this form, I have not given up any of my legal rights as a research participant.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT
(Can only be signed by an investigator or staff approved to administer consent)

_____
Printed Name of Administering Individual

_____ _____
Signature of Administering Individual Date

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October 05, 2021

MEMORANDUM FOR JOSHUA GRAY, Ph.D., DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY

SUBJECT: USU Institutional Review Board (IRB) (FWA 00001628; DoD Assurance P60001) Approval of Protocol USUHS.2020-040 for Human Subjects Participation

The Initial Review (Reference No. 922575) for your human subjects research protocol USUHS.2020-040, entitled "*A pilot study of N-acetylcysteine for alcohol use disorder*," was reviewed by the full Institutional Review Board on September 23, 2021 and Approved as minimal risk pending revisions. These revisions have been reviewed and approved by Edmund G Howe, MD, JD, Chair IRB. The date of this approval is October 04, 2021. This approval will be reported to the USU IRB #1 scheduled to meet on October 14, 2021.

FDA determination: Abbreviated IND.

Documents reviewed for this study:
1) EIRB Protocol Template, version 1.7
2) Informed Consent Document, version 1.10
3) Breathalyzer Consent, version 1.2
4) Phone Screen, version 1.5
5) Email template for upcoming phone calls, version 1.0
6) Email template for upcoming in-person appts 2-7, version 1.0
7) Email template for baseline appt, version 1.10
8) LOS from WRNMMC emergency department, version 1.0
9) Protocol Script, version 1.8
10) Assessment Appendix, version 1.7
11) Flowchart checklist, version 1.2
12) ATS email stating study team can visit ATS to recruit, version 1.0
13) COVID screen phone call, version 1.0
14) COVID screen questions, version 1.0
15) Business card for participants to give to their provider, version 1.0
16) CoC approval, version 1.0
17) Flyer, version 1.5
18) Physical and Mental Health Resources, version 1.1
19) Suicide Ideation Protocol, version 1.2
20) VR images, version 1.0
21) ATS LOS, version 1.0
22) IND sample label, version 1.1
23) FDA email correspondence, version 1.0
24) Letco capsule information, version 1.0
25) IND, version 1.0

26) Research monitor medical license, version 1.0
27) Pharmacy Impact Statement, version 1.0
28) Scientific Review Checklist_fillable_2019-02-twbCW_JCG (1), version 1.0
29) Study team documentation (CV, COI forms, CITI training certificates)

The Principal Investigator is required to provide study participants with a written statement regarding the research.

Should your project involve:

Accessing Defense Health Agency (DHA) databases, activities cannot commence until a DHA Data Sharing Agreement (DSA) has been executed.

Information Collections (e.g., surveys, focus groups, interviews), OMB clearance and/or RCS licensing may be required. Please work with the HRPP Office staff for assistance.

As a reminder, it is your responsibility to ensure all applicable protocol related approvals have been obtained prior to initiating study activities.

Authorization to conduct protocol USUHS.2020-040 will automatically terminate on 22 September 2022. If you plan to continue data collection or analysis beyond this date, IRB approval for continuation is required. Please submit an application for continuing approval to the IRB Office 60 days prior to your termination date.

You are required to: **report to the USU IRB after four (4) patients have completed the second in-person study visit, and when you implement the reporting SOP for Blood Alcohol Content (BAC) equal to or greater than 0.05**; submit amendments to this protocol, changes to the informed consent document (if applicable), adverse event reports, and other information pertinent to human research for this project. No changes to this protocol may be implemented prior to IRB approval. If you have questions regarding this IRB action or questions of a more general nature concerning human participation in research, please contact Nikolaos Tountas, PhD, at (301) 319-0445 or nikolaos.tountas.ctr@ushus.edu.

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Nikolaos Tountas, PhD
IRB Analyst
USU HRPP Office