Official Title:	Basis of sex-specific therapeutic responses to obstructive sleep apnea (OSA): a trial of N-acetylcysteine (NAC) in obstructive sleep apnea (OSA)
NCT Number:	NCT06311045
Study Number:	s23-01469
Document Type:	Informed Consent Form
Date of the Document:	• January 8, 2025

Research Subject Informed Consent Form

Title of Study:	Basis of sex-specific therapeutic responses to obstructive sleep apnea (OSA): a trial of N-acetylcysteine (NAC) in obstructive sleep apnea (OSA) i23-01469
Principal Investigator:	R. Nisha Aurora, MD, MHS Associate Professor of Medicine Division of Pulmonary, Critical Care, and Sleep Medicine NYU Grossman School of Medicine Joan H. Tisch Center for Women's Health, 159 E. 53rd Street 5th floor, NY, NY 10022 646-754-3300 Rashmi.aurora@nyulangone.org
Emergency Contact:	R. Nisha Aurora, MD 443-513-6535

1. About volunteering for this research study

You are being invited to take part in a research study. Your participation is voluntary which means you can choose whether or not you want to take part in this study.

People who agree to take part in research studies are called "subjects" or "research subjects". These words are used throughout this consent form. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. You may also decide to discuss this study and this form with your family, friends, or doctor. If you have any questions about the study or about this form, please ask us. If you decide to take part in this study, you must sign this form. We will give you a copy of this form signed by you for you to keep.

2. What is the purpose of this study?

The purpose of this research study is to evaluate the differences between men and women in how their bodies respond to a breathing problem during sleep called Obstructive Sleep Apnea (OSA). The study will help us to understand if there are differences between men and women with regards to what OSA does to the body – the biological stress and inflammation. To date, our research and other's research show that there are differences in the level of overnight stress between men and women. The supplement N-Acetylcysteine (NAC), may decrease this stress more in either men and women. This may help determine if different therapies need to be considered for men and women.

All subjects will use a machine called Autotitrating Positive Airway Pressure (APAP) nightly for about 3 months, as this is standard of care clinical therapy (first line therapy) for the treatment of OSA. We will first measure molecules in the blood before you go to sleep and after you wake up before treating your OSA. We will then measure these molecules (before and after sleep) after you have had about 3 months of treatment for your OSA with the APAP. These molecules will tell us about the level of inflammation and biological stress that your body is experiencing during your sleep.

After 12-18 weeks of APAP treatment, you will either receive 4 weeks of NAC or 4 weeks of placebo (a pill that contains no active ingredient). NAC is used as a dietary supplement to help reduce biological stress by increasing a molecule called glutathione (GSH) that is naturally found in our bodies and decreasing inflammation. It is used as a supplement in several conditions including lung conditions. There is evidence that in OSA this molecule is reduced and inflammation is increased. We are going to again compare the reduction of the inflammation and biological stress molecules between subjects who receive NAC and subjects who receive the placebo. We want to use this supplement to investigate to see if it helps the biological stress and inflammation seen with OSA and if there are difference between men and women with OSA with regards to the response to the supplement.

This study is a randomized study. This means, like flipping a coin, you will be assigned to receive either NAC or placebo. There are no special requirements or criteria to be in either group. You will have an equal chance of receiving NAC or placebo.

This study is called “double blind” because neither you nor the study staff knows if you are taking NAC or the placebo. The sponsor keeps records of which you are taking. The study staff can get this information if needed.

3. How long will I be in the study? How many other people will be in the study?

Your involvement in this study will last about 4-6 months. This will be an out-patient study. Your study visits will be at NYU Langone Medical Associates – Chelsea, Sleep Laboratory at 160 West 26th Street NY, NY 10001 and the Joan H. Tisch Center for Women’s Health, 159 E. 53rd Street, NY, NY 10022.

About 206 people will be in the study.

4. What will I be asked to do in the study?

If you choose to take part in this study, we will ask you to sign this consent form before you have any procedures with the study staff that are part of the study. Your participation in this study will last for 4-6 months and will involve 4 visits to the NYU Langone Medical Associates – Chelsea, Sleep Laboratory (2-3 visits) and the Joan H. Tisch Center for Women’s Health, 159 E. 53rd Street, NY, NY 10022. We will schedule these visits at a time that is convenient for you. One of the visits to the NYU Langone Medical Associates Sleep Laboratory is for an overnight sleep study.

Below is a list of each study visit that is part of the study. This list includes information about the research tests and procedures to be done at each visit and/or blood work to be taken. This section will help you understand what is expected of you at each visit.

Screening (expected to last one hour or less):

- The study team will inform you about the study.
- The study team will obtain your voluntary informed consent.
- We will ask you about your medical history, what medications you take - including over-the counter and prescription medications, vitamins or herbal supplements – and your tobacco, alcohol and drug usage.
- The HbA1c test is a blood test that measures your average blood sugar levels over the past 2-3 months. If you have not done this test in the last 6 months, we will collect 1 µL (less than ¼ teaspoon) of your blood to determine your HbA1c level using a Point of Care testing machine. The blood will be collected via fingerstick, placed into a very small tube and then inserted on the

cartridge for the testing machine. If your HbA1c level is less than 6.5%, we will proceed to screening.

Enrollment/Baseline Visit (Visit 1, Day 0 – overnight visit expected to last 12 hours)
Those who meet inclusion and exclusion criteria, who pass screening criteria, and give informed consent will be enrolled in the study and undergo the following assessments at Research *Visit 1*:

1. Polysomnography / sleep study will be performed. You will be asked to stay at the NYU Langone Medical Associates –Sleep Laboratory overnight one time.

2. We will use a measuring tape to check your waist and hip sizes. We will weigh you the morning after the sleep study.

3. Blood sampling: Blood samples will be drawn before and after the sleep study (pre- and post-sleep) at the NYU Langone Medical Associates –Sleep Laboratory. Approximately 3 tablespoons of blood will be collected each time.

4. An EndoPat device will be used to see how your blood vessels narrow or dilate, which tells us how healthy they are. The test will take approximately 20 minutes. It will be completed the morning after waking up from the in-laboratory sleep study. We will ask you to lay facing upward in a quiet environment with dimmed lighting. A single-use probe will be placed on the index fingers of each of your hands. A blood pressure cuff will be place on your other arm. After the procedure is complete, the probes will be removed and discarded.

5. You will complete 4 surveys or questionnaires. You are free to skip any questions that you prefer not to answer.
    - Epworth Sleepiness Scale (ESS): The ESS is an eight-item questionnaire on which you will be asked to rate your usual likelihood of falling asleep during each of eight common activities (ex: driving, watching television).
    - Insomnia Severity Index (ISI): The ISI is a seven-item questionnaire assessing the nature, severity and impact of insomnia. The questionnaire assesses severity of sleep onset, sleep maintenance, early morning awakenings, sleep dissatisfaction, and interference of sleep difficulties with daytime functioning.
    - Fatigue Severity Scale (FSS): The FSS is a nine-item measure of fatigue severity from a variety of medical and neurological disorders.
    - Pittsburgh Sleep Quality Index (PSQI): The PSQI is a 19-item questionnaire that is routinely used in both clinical and research settings to assess sleep quality over the proceeding month.

6. After the first in-laboratory sleep study, you will be started on your Positive Airway Pressure (PAP) machine as was planned for your OSA (standard of care). We will follow up with you by phone each week to see how the PAP machine use is going for you. After each night, data from your PAP machine are transmitted to the manufacturer's HIPAA-approved, secure PAP adherence server. This information is followed by your doctor as part of your clinical care. The research team will review these transmitted data.

Visit 2 (Day 84 to 126 -)
After 12 weeks of APAP therapy, procedures 2-6 above from the Baseline/Visit 1 will be repeated at Visit 2. For your evening blood draw, a phlebotomist will come to your place of residence for the collection.

The team will arrange the data and time with you. You will then come in the next morning for another blood draw, the EndoPat assessment and survey completion.

Randomization to intervention versus placebo will be done at the end of Visit 2. Participants will continue on PAP therapy after this visit. Whether you are on supplement or placebo, you will take the medication twice a day (morning and evening) with a glass of water for 4 weeks total.

Final Study Visit - Visit 3 (Day 112 to Day 154 -)
After 4 weeks of intervention versus placebo, procedures from visit 2 will be repeated:

- Adverse events will be recorded.
- Any residual supplement will be collected and recorded.
- You will be provided a copy of their baseline sleep study from Visit 1.

Biospecimen Storage for Future Research
The purpose of future research is to continue analyzing the samples for inflammation and oxidative stress biomarkers with potential new techniques not available at present. Samples will be stored at NYU Langone Medical Associates – Chelsea and NYU Langone Translational Lung Biology Laboratory, Division of Pulmonary and Critical Care Medicine, 550 First Ave, MSB-594. Sample storage is optional. Samples will be stored for 20 years.

Samples will be coded and only the NYU PI will have access to the linking key between subject ID and subject identity. Only those authorized by the PI will have access to the samples. We will not perform genetic testing in a certified lab testing to diagnose your predisposition to conditions you don't currently know you have. You can withdraw your samples from banking by contacting the PI.

Identifiers will be removed from your identifiable data and specimens. After such removal the data and specimens may be used for future research studies or shared with other researchers and we will not request additional informed consent from you to use these data and specimens as we have noted here.

Please initial next to your choice below:

_____ Yes, I agree to allow my samples to be used for future research as described above.

_____ No, I do not agree to allow my samples to be used for future research as described above.

5. What are the possible risks or discomforts?

N-Acetylcysteine (NAC): The proposed dose of 600 mg twice daily (1200 mg total daily) NAC is not known to cause any significant adverse reactions. This supplement is available over the counter and is routinely used with a good safety profile. Side effects are unusual, but may include nausea, vomiting, diarrhea, transient skin rash, flushing, epigastric pain, and constipation. These side effects are generally seen in 1 out of 10 persons. You will be monitored for side effects during the duration of NAC use.

Sleep study: There are no major risks from a sleep study. You may experience inconvenience and psychological discomfort while sleeping in an unfamiliar environment. You may also experience minor discomfort from the monitoring equipment.

Blood draws: The potential risks of blood draws may occasionally include pain, bruising, or a small infection at the puncture site. Sometimes a small amount of bleeding into the arm (hematoma) may occur. Risks also include fainting or feeling faint. Tell the study staff right away if you feel faint.

Hemoglobin A1c test: Risks associated with this test are rare, given the small quantity of blood used. Risks include pain and bruising at the puncture site.

Surveys: You may experience mild fatigue or test performance anxiety when completing surveys. You may also experience frustration that is often experienced when completing surveys. Some questions may be of a sensitive nature, and you may therefore become upset as a result. If, however, you become upset by questions, you may stop at any time or choose not to answer a question.

EndoPat: Risks associated with this test are minor and include numbness, tingling or slight discomfort at the site of the blood pressure cuff during and post-inflation. These sensations are temporary and resolve within 2–3 minutes.

Placebo: The placebo capsules will match NAC. This matching, allergen-free placebo will be created by filling empty capsules of the same size and color with a sugar powder. As with NAC (above), the Investigative Pharmacy at NYU will acquire the placebo capsules. The placebo capsule is not active. Placebo is safe and routinely used in research studies. The rare side effects include nausea, drowsiness, and allergic reactions.

6. What if new information becomes available?

During the course of this study, we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

7. What are the possible benefits of the study?

You will not benefit directly from taking part in the study. However, your participation in the study may help us understand if OSA has different effects on the body on men and women.

8. What other choices do I have if I do not participate?

During the course of this study, we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

9. Will I be paid for being in this study?

You will be paid $250 for the completed in-laboratory PSG of Research Visit 1. If you choose to leave or are withdrawn from the study for any reason before finishing the entire study, you will be paid for the completed in-laboratory PSG. You will be paid $50 for Research Visit 2 and $50 Research Visit 3. You will receive payment within 1 week after your last study visit. If you complete all the study visits, you will receive $350.00 for being in this study.

As is required by the laws that apply to NYU Langone Health, in order for you to receive a payment (i.e. check, ClinCard, or bank gift card), you need to give the study staff either your Social Security number

or your Alien Registration number and will be asked to complete an IRS W9. If you do not have either of these numbers or are not willing to complete the IRS W9, you may be in the study but will not receive any payment.

You must let us know immediately if/when the total research payments presently equal or are likely to exceed $600.00 total (not including travel reimbursements) for each calendar year. If your total payments (for one or more studies) reach $600.00, please tell the PI on page 1. However, you are required to report to the IRS all payments made to you by NYU Langone for your participation in any research for this calendar year, even payments under $600.00.

In order to receive payments for your participation in research, you may need to provide your Social Security number. This is because NYU Langone Health is required to report to the Internal Revenue Service (IRS) any amounts that are paid to research participants that are equal to or greater than $600.00. If you will receive payments in any amount by a check, you will need to provide your Social Security number or Alien Registration number and will be asked to complete an IRS W9. If you do not have either of these numbers or are not willing to complete the IRS W9, you may be in the study but will not receive any payment.

Biospecimens collected for the purposes of this research (even if identifiers are removed) may be used for commercial profit. If your biospecimens are or become commercially profitable, you will not share in this commercial profit.

10. Will I have to pay for anything?

You and/or your health insurance will not be billed for the costs of the N-Acetylcysteine nor for the tests and procedures required solely for this study.

You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs or you do not have insurance, these costs will be your responsibility.

11. What happens if I am injured from being in the study?

For medical emergencies contact 911. If you think you have been injured as a result of taking part in this research study, tell the principal investigator as soon as possible. The principal investigator's name and phone number are listed at the top of page 1 of this consent form.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for NYU Grossman School of Medicine or NYU Langone Health to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

12. When is the study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped or your participation ended at any time by your physician, the study sponsor, or the U.S. Food and Drug Administration (FDA) without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The study sponsor, the principal investigator, the FDA, or other body responsible for monitoring the safety of the study has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Leaving the study will not interfere with your future care, payment for your health care or your eligibility for health care benefits.

13. How will you protect my confidentiality?

Your medical information is protected health information, or "PHI", and is protected by federal and state laws, such as the Health Insurance Portability and Accountability Act, or HIPAA. This includes information in your research record as well as information in your medical record at NYU Langone Health. In compliance with NYU Langone Health policies and procedures and with HIPAA, only those individuals with a job purpose can access this information.

Medical information created by this research study may become part of your medical record. We may include your research information in your medical record for several reasons, including for the billing of services provided in connection with the study, to securely document any medical services you receive, and so that other members of the NYU Langone Health community who may treat you have access to important information about your health.

You have a right to access information in your medical record. In some cases, when necessary to protect the integrity of the research, you will not be allowed to see or copy certain information relating to the study while the study is in progress, but you will have the right to see and copy the information once the study is over in accordance with NYU Langone Health policies and applicable law.

Certificate of Confidentiality

To help us further protect your confidentiality, this research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The NIH has issued a Certificate of Confidentiality for this research. This adds special protection for the research information (data, documents, or biospecimens) that may identify you.

Research information protected by this Certificate of Confidentiality cannot be disclosed to anyone else who is not connected with the research, without your consent. With this Certificate of Confidentiality, the researchers may not disclose or use research information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, without your consent. However, disclosure, without your consent, is still necessary if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases).

The Certificate of Confidentiality cannot be used to refuse a request for information from appropriate government agencies responsible for project oversight.

The Certificate of Confidentiality does not prevent you from releasing information about yourself and your involvement in this research, including for your medical treatment. Federal regulations may also allow for the use or sharing of information for other scientific research.

By agreeing to be in this research and signing below, you are giving your consent to share research information with others at NYU Langone Health. This means that your research information, including lab results, , information about the supplement used in this study, may be included in your NYU Langone Health electronic medical record.

14. HIPAA Authorization

As noted in the Confidentiality section above, federal law requires us, and our affiliated researchers, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions. We are asking for your permission (authorization) to use and share your health information with others in connection with this study- in other words, for purposes of this research, including conducting and overseeing the study.

Your treatment outside of this study, payment for your health care, and your health care benefits will not be affected even if you do not authorize the use and disclosure of your information for this study.

What information may be used or shared with others in connection with this study?
All information in your research record for this study may be used and shared with those individuals listed in this section. Additionally, information in your medical record that the research team believes may be important to the study may be accessed by those listed here. This includes, for example, results from your physical examinations, laboratory tests, procedures, questionnaires, and diaries.

Who may use and share information in connection with this study?
The following individuals may use, share, or receive your information for this research study:

- The research team, including the Principal Investigator, study coordinators, and personnel responsible for the support or oversight of the study
- The study sponsor: The National Heart, Lung, Blood Institute (NHLBI)
- Governmental agencies responsible for research oversight (e.g., the U.S. Food and Drug Administration or FDA).
- Health care providers, including your doctors and others who provide services to you in connection with this study, and laboratories or other individuals who analyze your health information in connection with this study.
- Other study sites involved in the research

Your information may be re-disclosed or used for other purposes if the person who receives your information is not required by law to protect the privacy of the information.

What if I do not want to give permission to use and share my information for this study?
Signing this form is voluntary. You do not have to give us permission to use and share your information, but if you do not, you will not be able to participate in this study.

Can I change my mind and withdraw permission to use or share my information?
Yes, you may withdraw or take back your permission to use and share your health information at any time for this research study. If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. To withdraw your permission, send a written notice to the principal investigator for the study noted at the top of page 1 of this form. If you withdraw your permission, you will not be able to stay in this study.

How long may my information be used or shared?

Your permission to use or share your personal health information for this study will never expire unless you withdraw it.

15. Electronic Medical Record and Release of Study-Related Information

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of your medical chart within NYU Langone Health. An EMR is simply a computer version of a paper medical record.

If you are or have been a patient at NYU Langone Health in the past, you have an EMR at NYU Langone Health. Information from your research participation will be added to this EMR.

If you have never been a patient at NYU Langone Health, you may not have an EMR at NYU Langone Health. In connection with your participation in this study, an EMR will be created for you. The purpose of your EMR at NYU Langone Health will be to facilitate this research study and allow the researchers to maintain information arising from your participation in this research study. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility, for example, your name, the name of your primary doctor, the type of insurance you have, your date of birth and other health-related information.

What may be placed in the EMR?
Information related to your participation in the research (e.g., laboratory tests, research-related notes, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by NYU Langone Health.

This information will be accessible to other members of the NYU Langone workforce that are not part of the research team. Information within your EMR may also be shared with others who NYU Langone Health has determined may appropriately have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Will I have access to research-related information within the Electronic Medical Record?

In this study, some research-related information will never be made available to you in your EMR. None of this information will not be accessible in your EMR because the information is specific to this research and not part of your clinical care. ***None of the results from this study will be placed in the medical record. that includes the blood that was drawn as part of the study, the EndoPAT procedure, , the sleep study, and the surveys will not be placed in your EMR.***
We will give you a copy of your first sleep study if you want it for your own records. It will not be part of the EMR.

16. The Institutional Review Board (IRB) and how it protects you

The IRB reviews all human research studies – including this study. The IRB follows Federal Government rules and guidelines designed to protect the rights and welfare of the people taking part in the research studies. The IRB also reviews research to make sure the risks for all studies are as small as possible. The NYULH IRB Office number is (212) 263-4110. The NYULH IRB is made up of doctors, nurses, scientists, and people from the community.

17. Who can I call with questions, or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on the top of page 1 of this consent form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Institutional Review Board (IRB) at (212) 263-4110.

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

NYU Langone Health is committed to providing a safe, productive, and welcoming environment for participants and researchers in all research studies and interactions. All participants will be treated with respect and consideration, and in turn, we ask that you please treat fellow participants and research staff with respect.

Please refer to the NYU Langone Statement on the Conduct of Participants in Research Studies for further information.

When you sign this form, you are agreeing to take part in this research study as described to you. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer.

Name of Subject (Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Print)	Signature of Person Obtaining Consent	Date

Witness to Consent Process for Non-English-Speaking Subjects (using a translated consent form OR "Short Form" in Subject's Spoken Language)

Statement of Witness
As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name of Witness (Print)	Signature of Witness	Date

Witness to Consent of a Subject Who Cannot Read or Write

Statement of Witness
I represent that the consent form was presented orally to the subject in the subject's own language, that the subject was given the opportunity to ask questions, and that the subject has indicated his/her consent and authorization for participation by (check box that applies).

- ☐ Subject making his/her own "X" above in the subject signature line
- ☐ Subject showed approval for participation in another way; describe:

Name of Witness (Print)	Signature of Witness	Date