UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

Protocol Title:	Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea on Sympathetic and Vascular Function (CARDIOSA-12)
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Funding Sponsors:	American Heart Association American Sleep Medicine Foundation

Summary

You are being invited to participate in a research study. Your participation is voluntary and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have about participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time, please contact the Institutional Review Board (IRB) at (215) 898-2614.

The research study is being done to look at the effect of tongue stimulation on blood pressure and heart-related measures in people who have obstructive sleep apnea.

If you agree to join the study, you will be asked to complete the following research procedures:

- 2 in-lab cardiovascular testing sessions (5 visits to our office/lab in total)
- 2 at-home blood pressure and sleep testing sessions
- 2 weeks of no Inspire® device use
- 1 month of regular Inspire® use
- 1 month of very low level Inspire® use

Your participation will last for about 2½ months.

The most serious risk of participation is your sleep apnea getting worse while your Inspire implant is turned very low or off. This could raise your risk of high blood pressure, heart attack, stroke, sleepiness, and falling asleep while driving or using heavy machinery. Please note that there are other factors to consider before agreeing to participate, such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a

member of the study team will review the full information with you. You are free to decline or stop participation at any time.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you have obstructive sleep apnea and a nerve stimulator implant. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. 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. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, and/or family doctor. You may find some of the medical language difficult to understand. Please ask the investigator and/or the research team about this form. If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The hypoglossal nerve controls tongue movement. The Inspire® sleep implant works by stimulating this nerve. This process is called hypoglossal nerve stimulation, or "HGNS." In this study, we are interested in seeing how HGNS affects blood pressure and heart-related measures and if it lowers the risk of heart problems in people with obstructive sleep apnea.

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

Your participation in this study would last for about 2½ months. We plan to include about 60 people.

How do I qualify to be in this study?

- You must have a nerve stimulator (HGNS) implant.
- Before enrolling in the study, you must use your HGNS for at least 20 hours per week on average.
- You must not have had a fall-asleep accident or "near miss" while driving in the year before HGNS implantation.
- You must be willing to temporarily stop HGNS therapy (a "washout"), which may lead to your sleep apnea symptoms coming back. During this time period, you cannot use CPAP (Continuous Positive Airway Pressure: a machine that blows air through a mask to keep your breathing airway open) or other sleep apnea treatment. See the study timeline below for more information.
- Women of child bearing potential: you must NOT be pregnant or plan to become pregnant. This study involves temporarily stopping treatment of obstructive sleep apnea, which may harm an unborn baby. If you decide to enroll in the study, you will need to take a urine pregnancy test after enrollment (prior to washout #1), and again before washout #2.

What am I being asked to do?

If you decide to participate, we will test your cardiovascular function (described below) after a period of regular ("active") Inspire treatment and after a period of very low ("sham therapy") Inspire

treatment. You will be blinded during both "sham" and "active" periods, which means that you will not be told which level of treatment you are having.

There will be 5 visits in total, which will take place on Days 1, 8, 36, 43, and 71.

Before Starting the Study:

- Use your Inspire HGNS device normally, as directed by your doctor (at least 20 hours per week).

Study Days 1-7 (Week 1) – Enrollment and Washout:

- Enrollment visit (Day 1): If you wish to be in the study, you will be asked to sign this Informed Consent Form. You will also fill out some questionnaires about your sleep, health, lifestyle/habits, medications, and/or device use, and take 2 computerized tests.
- No device use ("washout period"): Your HGNS device will be deactivated (turned off) for 1 week.

Study Days 8-35 (Weeks 2-5) – Active or Sham Therapy, Part 1:

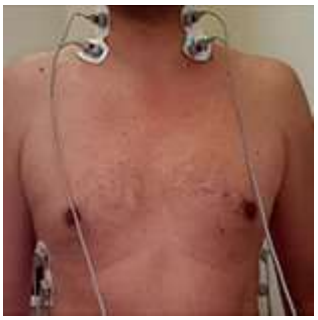
- Randomization visit (Day 8): At this visit, you will be randomly assigned (like the flip of a coin) to receive either the "active" (Inspire therapy) or "sham" (very low level therapy) first.
    - Based on this assignment, you will use active or sham therapy at home for the next 4 weeks (about 1 month). You will not be told which level of therapy you are using.
- You will fill out some questionnaires again.
- At-home blood pressure and sleep tests (Days 34-35): We will mail you a blood pressure cuff and a home sleep test. You will wear the blood pressure cuff on your arm for 24 hours. For 1 night, you will also wear a watch-like device on your wrist and finger to measure your blood flow and oxygen level. The devices look like this:

Study Days 36-42 (Week 6) – Cardiovascular Testing and Washout:

- In-lab cardiovascular testing (Day 36):
    - You will bring the blood pressure and sleep watch equipment with you to the lab.
    - You will fill out questionnaires and take 2 computerized tests.

- Blood flow recording: We will record blood flow through your body by passing an ultrasound wand over the arteries in your arm, neck, and groin. You will wear a blood pressure cuff, which will be inflated for 5 minutes. You may be seated or lying down for this test. This test is non-invasive and takes about 10 minutes.

- Heart contraction measurement: You will wear sticky pads on your neck and body, attached to wires (like an EKG) that record your heart rhythm and chest movement. You will be lying down for this test. This test is non-invasive and takes about 15 minutes.



- Washout period (Days 36-42): Your device will be deactivated (turned off) again for 1 week.

Study Days 43-70 (Weeks 7-10) – Active or Sham Therapy, Part 2:

- Home use of active or sham therapy: You will have either sham or active Inspire therapy (whichever one you did *not* have before, during Part 1) at home for the next 4 weeks (about 1 month). Again you will not be told which level of therapy you are using.
- You will fill out questionnaires.
- At-home blood pressure and sleep tests (Days 69-70): We will mail you a blood pressure cuff and home sleep test again. Again you will wear the blood pressure cuff on your arm for 24 hours. For 1 night, you will also wear the watch-like device on your wrist and finger to measure your blood flow and oxygen level.

Study Day 71 (Week 11) – Last Visit:

- In-lab cardiovascular testing: *(same as on Day 36)*
  - Bring back the blood pressure and sleep watch equipment
  - Have blood flow recording
  - Have heart contraction measurement
  - Fill out questionnaires
  - Take 2 computerized tests

After Last Study Visit:

- Go back to using your Inspire device normally, as directed by your doctor.

Medical record: We will also look in your medical record to collect information such as your age, sex, race, height, weight, whether you have been diagnosed with high blood pressure or diabetes, and the results of your routine care sleep tests, clinical follow-up visits, and other lab tests.

What are the possible risks or discomforts?

Blood Pressure Machine: The 24-hour blood pressure measurement device is well tolerated. It is lightweight and padded and generally does not disturb sleep or any other daily activities. If your blood pressure reaches unsafe levels, Dr. Dedhia may suggest that you contact your primary care physician and/or ask you to go to the emergency room.

Sleep testing: Wearing the sleep test device could lead to you not sleeping as well as usual on the night of the test.

Blood flow measurements: During one of the blood flow tests, the cuff will stay inflated for 5 minutes. This can result in temporary feelings of numbness and "pins and needles" in the arm that last for 1 or 2 minutes. This is generally well tolerated and causes no long-term side effects. However, if you get too uncomfortable and need to stop, the cuff can be deflated (let the air out) or taken off.

Untreated Sleep Apnea: As part of this study, your nerve stimulator will be completely deactivated (turned off) for a total of 14 days. In addition, you will spend 28 days on "sham therapy," which is unlikely to help treat your apnea. While untreated, your apnea and symptoms will return to baseline (the way you felt before treatment). You will be at higher risk of developing serious medical conditions including but not limited to: high blood pressure, heart attack, or stroke. You may also experience morning headaches, snoring, and excessive daytime sleepiness. **Excessive daytime sleepiness may put you at risk for serious injury or death while operating heavy machinery or motor vehicles. You should use extreme caution or completely avoid doing these activities while enrolled in this study.**

There is also a risk that someone could get access to the information we collect about you. We will do everything we can to protect your privacy, but it is not possible to guarantee total privacy.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, 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.

What are the possible benefits of the study?

This study is not designed to benefit you directly. Your obstructive sleep apnea may improve while you are in this study, but it may not. We expect that your symptoms will get worse during the parts of the study in which your device is turned off or to a low "sham" setting. The study results may help doctors to better understand sleep apnea and might be used to help people with sleep apnea in the future.

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

If you choose not to participate in this study, it will not affect your medical care or your relationship with your health care providers. You should still go to all of your regular doctors' appointments as scheduled. You may wish to talk to your doctor about whether or not to participate. If you are a

student or employee of the University of Pennsylvania, your decision will not affect your standing at the university in any way.

Will I be paid for being in this study?

You will be offered $100 payment after each of the 5 study visits, and $10 for parking after each of the 2 in-lab cardiovascular testing visits (total = up to $520). You will not have to pay for any testing, since it is being done outside of routine clinical care.

Your payments will be in the form of mailed checks and/or a ClinCard. The study team will discuss these payment options with you in more detail.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Also, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I receive the results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results will not be returned to you because they will not be relevant to your health care.

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

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 the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed on page 1 of this form. If you get treatment for your injury from a doctor who is not involved in this study, make sure to tell them that you are taking part in a research study.

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 at any time by the study's Principal Investigator, your doctor, the study Sponsors, or the 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 Sponsors or Principal Investigator have decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. The information we collect from you will be labeled with a code number instead of your name. Paper files will be kept in a secure location that only the study team can access. Electronic files will be on a secure, password-protected computer, so that only the study team can access it. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the FDA, they may review your research records.

What information about me may be collected, used, or shared with others?

- Name, address, email address, and/or telephone number
- Date of birth
- Demographic information (for example: age, sex, race)
- Medical record number
- Medical and surgical history
- Results from physical examinations, lab tests, scans, and/or procedures
- Device identifier or serial number
- Social Security Number (in order to pay you for participation)

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- see if the research was done right
- evaluate and manage research functions

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- Study Investigators and their study team
- Data and safety reviewing entities at the University of Pennsylvania
    - The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects)
    - The University of Pennsylvania Office of Clinical Research

Who, outside of the School of Medicine, may receive information about me?

- Authorized members of the University of Pennsylvania, University of Pennsylvania Health System, and/or School of Medicine workforce who may need to access your information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, for accounting or billing matters, etc.)
- Other authorized personnel at Penn, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB
- The funding sponsors and organizations supporting the sponsors

Oversight organization

- The U.S. Office of Human Research Protections

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

What happens to my information collected for this study?

Your identifiable information will be stored for future research purposes. Future researchers may receive information that could identify you. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

The following identifiers will be retained with your information: name, date of birth, medical record number, and device implant serial number. Your information may be stored and used for future research purposes for an indefinite amount of time. There are no plans to tell you about any of the specific research that will be done. Possible future research may include additional studies about active vs. sham Inspire therapy or cardiovascular changes. We may share your identifiable information with: other research, academic, and medical institutions, other researchers, and the study sponsors. We will not follow up with you to tell you about the specific research that will be done. We will not give you any results from these studies. It is possible that you may have chosen not to participate in these future research studies, had you been approached for participation.

There is a risk of breach of confidentiality (unintentional release of your information). We will do our best to make sure that this doesn't happen. However, we cannot guarantee total privacy. We will protect your confidentiality during storage and sharing by using code numbers instead of your name wherever possible.

You will likely not directly benefit from future research with your information. Research with your identifiable information may help others by improving our understanding of health and disease, improving health care and making safer or more effective medical therapies, and developing new scientific knowledge.

If you have questions about the storage of your information, or have changed your mind, you can contact Dr. Dedhia at (215) 360-0379.

Will information about this study be available to the public?

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

Electronic Medical Records and Research Results
What is an Electronic Medical Record and/or a clinical trial management system?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record. A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of research.

If you have never received care within UPHS and are participating in a University of Pennsylvania

research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures done as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to collect 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). Results of research procedures done as part of your participation in the study (for example: laboratory tests, imaging studies, and clinical procedures) may be placed in this EMR.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (for example: laboratory tests, imaging studies, and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

Once placed in your EMR or in the CTMS, these results are accessible to appropriate UPHS workforce members who are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g., health insurance company, disability provider, etc).

Who can I call with questions, complaints, 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 page 1 of this 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 Office of Regulatory Affairs at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	_____
Name of Participant (Please **Print**)	Signature of Participant	Date
_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature of Person Obtaining Consent	Date