Permission to Take Part in a Human Research Study

Northwestern University
Department of Otolaryngology

Consent Form and HIPAA Authorization for Research

Title of Research Study:Towards a Self-Administered Hearing Protection Regimen
Short Title: Oral Statins and Hearing Loss (STU00212929)

Investigators:
Donna Whitlon, PhD – Principal Investigator, Northwestern-Feinberg School of Medicine
Alan Micco, MD – Northwestern Memeorial Hospital, Northwestern Medicine

Supported By: This research is supported by the Army Congressionally Directed Medical Research Program (CDMRP).

Financial Interest Disclosure: The following disclosure is made to give you an opportunity to decide if this relationship will affect your willingness to participate in this research study.

Two of the study investigators (Drs. Whitlon and Richter), who will not be your treating physicians, are inventors on patents aimed at using statin drugs to prevent or repair noise induced hearing loss. Because of this patent, there is potential for future financial profit to the inventors as well as to Northwestern University, the owner of the patents, as a result of the knowledge gained from this study.

Your doctor (Dr. Micco), who is also responsible for this research study, has no financial interest in this knowledge. He is interested in both your clinical care and the conduct of this research study. You have the right to discuss this study with other persons who are not part of the research team before deciding whether to participate in the research.

Key Information:
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?
You are reported to be a patient who suffers from sudden hearing loss (Idiopathic Sudden Sensorineural Hearing Loss) [ISSNHL] and who apparently meets the inclusion criteria for participation in a research study.

While you receive the standard care for ISSNHL, we will test whether the addition of an oral drug called lovastatin would help you recover from your type of hearing loss. While lovastatin has been approved for many years for other purposes, lovastatin is not FDA approved for the purpose of this study.

What should I know about a research study?
- Someone will explain this research study to you.
- Whether or not you take part is up to you.

- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.
- You will still receive the standard of care if you do not participate in the study.

Why is this research done?

The overall purpose of this research is to determine whether lovastatin, when combined with standard care, will improve hearing for your type of hearing loss compared to those subjects who get standard care alone (no lovastatin).

Background: Sound travels through the outer ear canal to the cochlea. The cochlea is a snail-shaped structure in your temporal bone, and is situated at the sides and base of the skull. Sound is energy that vibrates the delicate structures within the inner ear.

ISSNHL is diagnosed when a) the hearing loss comes on over a very short period of time, usually 72 hours; b) there is a loss of hearing, usually 30 decibels (a measure of extent of the sound loss), at 3 sound frequencies (loosely related to pitch) tested consecutively; and c) all known causes for ISSNHL have been ruled out. Athough the exact mechanisms that initiate and cause this hearing loss are unknown, there exist several ongoing theories for that damage, all of which finally result in the cells within the cochlea giving in to damage.

The standard care for ISSNHL is oral steroid such as methylprednisolone or intratympanic steroid (dexamethasone-injected through the ear drum) The published data on the outcomes of these treatments is difficult to compare since the studies may not be standardized and the outcome after steroid treatment results in about 1/3 of patients fully recovering their hearing, 1/3 of patients only partly recovering, and 1/3 of patients not recovering during the study period. This study is being done to determine whether lovastatin, in addition to the standard care is better, no different, or worse when compared to the standard care treatment alone.

Studies in animals have shown that a statin given directly to the cochlea, protects hearing from damage due to exposure to high level noise and there is evidence that oral lovastatiin may also provides some protection of hearing after high level noise exposure.

How long will the research last and what will I need to do?

At each study visit, you will have your hearing and speech understanding tested, and will answer a questionnaire regarding tinnitus (ringing or similar sound in the ear) symptoms. The exact length of your study participation depends on the outcomes of your treatments. The longest the study can take after your diagnosis for ISSNHL is approximately 4.5 months, depending on outcome This is similar to the amount of time and frequency of visits that you would likely undergo if you were not on the study.

More detailed information about the study procedures can be found under the section **what happens if I say, "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

The risks related to lovastatin are explained in detail below in the section **"Detailed Risks: Is there any way being in this study could be bad for me?".** Although risks for lovastatin are less likely to occur because you receive the drug for only one week, there there are rare risks for serious muscle damage called rhabdomyopathy; for liver damage; and for diabetes.

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Will being in this study help me any way?

The research aims to determine if there is improved recovery from ISSNHL with lovastatin, but the effect of lovastatin on human hearing loss is not known. If you take part in this study, your condition may improve, may not change or may worsen, and no guarantee can be made. You may benefit by an improvement in hearing, but it is also possible that lovastatin will not have an additional beneficial effect over that of standard care alone. Information learned from this study may help others in the future who have ISSNHL

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You decide whether or not to participate. If you choose to not participate, there will be no penalty to you or loss of benefits to which you are entitled.

Instead of being in this study, your choices may include:

- Treatment with the standard of care as advised by your doctor
- No treatment

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Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Whom can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at Northwestern Univeristy:

Dr. Alan Micco, MD
Department of Otolaryngology
Northwestern Medicine
675 N. St. Clair
15-200
Chicago, IL 60611
Phone: 312-695-8182

Dr. Donna Whitlon, PhD
Department of Otolaryngology
Northwestern University
323 E. Superior Street
Chicago, Il 60611
Phone 312 503 1603
e-mail: whitlon@northwestern.edu

This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.

- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?

We plan to enroll 100 participants, 50 males + 50 females in this research study.

What happens if I say "Yes, I want to be in this research"?

You visited the clinic because of your sudden hearing loss. If the clinical examination, hearing testing, speech understanding testing and tinnitus self assessment indicate that the hearing loss originates from a malfunction of your inner ear and nerves connected to it, but the cause is unknown, you will likely be diagnosed with ISSNHL.

If you appear to qualify for consideration as a participant in the study, you will be asked if you are interested in hearing about the information related to participating in this research study. A study coordinator will explain the entire study to you and will answer any questions you may have. After you have agreed to participate in the study by signing this Consent Form, you will be randomized to receive lovastatin or placebo. The experimental treatment (lovastatin or placebo) you get will be chosen by chance, like flipping a coin. Neither you nor the study doctor will know or choose what treatment you get. You will have an equal chance of being given either lovastatin or placebo. Regardless of randomization, all subjects will still receive standard care during the study.

A prescription will be written for you to take to a regular pharmacy for oral methylprednisolone. Another prescription wil be written for you and given to the study coordinator to fill for either lovastatin or placebo (looks like the lovastatin capsule but has no lovastatin in it). Using a mathematical formula, the pharmacy will determine which subjects are given lovastatin, and which ones are given placebo. The pharmacy will fill the prescription and the study coordinator will retrieve it and have it for you to pick up. you will take your first dose of lovastatin or placebo as soon as you receive it.

This study drug will be in addition to the prescription your doctor gives you to fill the methylprednisolone standard of care prescription and which is taken as a pill, with the dose decreasing gradually for 11 days. Patients on the study are prescribed a 7 day course of a statin or a placebo to be taken orally for 7 days with the methylpredisolone. This study follows the treatments timeline with the steroids that all patients of Dr. Micco diagnosed with ISSNHL follow in the clinic.

Should you start the study by later be found by a delayed MRI to have abnormalities on the scan, you will be contacted and taken off the study.

At every clinic visit, you will see the doctor, have your hearing and speech understanding tested and take a self assessment tinnitus evaluation.

The timing of the study visits will depend on your response to your therapy.

If you take part in this research, you will be responsible to:

- Attend all study visits, tests and tinnitus questionaires

- To follow the directives given by your study doctor, and to acquire and take the standard medications and lovastatin or placebo as instructed.
- To tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study.
- You must tell the study doctor or nurse before enrolling in any other clinical trials while on this trial.
- To avoid interacting drugs as described in a list provided by the study team [Be sure to submit the list of interacting drugs to the IRB that you will provide to subjects.] and to avoid grapefruit juice for the first 10 days of the study and to report all drugs that you are taking during the study.
- To take precautions against pregnancy during the trial as described in this Consent Form.
- Report any muscle pain, muscle tenderness or muscle weakness to your study doctor immediately

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time; it will not be held against you. Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefits to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Detailed Risks: Is there any way being in this study could be bad for me?

There are important drug interactions between lovastatin and other drugs. The list of interacting drugs provided to you includes the most important interacting drugs.

Not all of the side effects seen with lovastatin are listed below. [Disclose all of the risks described in the Patient Counseling section of the package Insert or justify why not for those you propose to omit (if any)]

There is a risk of serious or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all the medications you are taking before you start the study and also before starting any new medications (except in case of emergency) while on the study.

Lovastatin is contraindicated during pregnancy and in nursing mothers because cholesterol and possibly other products of the cholesterol biosynthesis pathway are essential components for fetal development. Lovastatin should not be administered to women of childbearing age only when such patients are highly unlikely to conceive.

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma

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The risk of myopathy/rhabdomyolysis is dose related. In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4933 patients randomized to lovastatin 20 to 40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily.

The risk of myopathy7/rhabdomyolysis is increased by concomitant use of lovastatin with the following:

Strong inhibitors of CYP3A4: including itraconazole, ketoconazole, Posaconazole, voriconazole, erythromycin and clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodine or cobicistat containing products. Combination of these drugs is contraindicated
.
The combined use of lovastatin with gemfibrozil should be avoided

Caution should be used when prescribing other fibrates or lipid-lowering doses (>1g/day) of niacin with lovastatin as these agents can cause myopathy when given alone.
The use of lovastatin with cyclosporin should be avoided.

The use of lovastatin at more than 20 mg with danazol, diltiazem, dronedarone or verapamil should be avoided.

The combined use of lovastatin at doses higher than 40 mg with amiodarone should be avoided.

Cases of myopathy, including rhabdomyolysis have been reported with lovastatin coadministered with colchicine and caution should be exercised.

The risk of myopathy, including rhabdomyolysis may be increased by concomitant administration of ranolazine.

Avoid grapefruit juice.

There have been rare reports of immune-mediated necrotizing myopathy and anutoimmune myopathy, associated with statin use.

Liver dysfunction. Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least a year in early clinical trials. The increases usually appeared 3-12 months after the start of therapy with lovastatin.

Lovastatin should be used with caution in patients who consume substantial quantitites of alcohol or who have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

Increases in HbA1c and fasting serum glucose levels have een reported with HMG-CoA reductase inhibitors, including lovastatin.

<u>Lovastatin</u>
<u>The brief exposure to lovastatin likely reduces the possibility for most of the following side effects to occur:</u>

- Muscle damage. There is a risk of rare, but serious, muscle problems that can lead to kidney problems, including kidney failure and rarely, death.
- Liver damage. There are rare, but serious liver problems that may be manifested by [Insert lay terms for symptoms and abnormal labs].
- Diabetes mellitus. Increases in blood sugar and [Insert lay terms for manifestations/symptoms of diabetes].
- Be sure to let your study doctor or study nurse know immediately if you develop any of these following problems:
    - Persistent weakness, muscle tenderness, or pains that happen without a good reason, especially if you also have a fever or feel more tired than usual
    - Nausea and vomiting
    - Brown or dark-colored urine
    - Feeling more tired than usual
    - Skin and whites of your eyes become yellowish
    - Stomach pain

Other problems that have been caused by lovastatin include headaches, skin rash (which rarely may be severe), severe allergic reaction (a hypersensitivity to a substance that can include severe respiratory symptoms) or swelling of the legs and ankles , constipation, gas, diarrhea, pain or numbness in arms or legs, tendon rupture (a trauma to the fibrous tissue that attaches muscle to bone), urinary tract infection (infection to any part of the urinary system including kidneys, ureters, bladder or urethra) dizziness, memory impairment and depression.

Unknown Risks

Other side effects that are not known at this time could happen. During the study, you will be told about any new information that may affect your decision to stay in the study. If you decide to stay in the study after learning of new information, you will be asked to sign an updated consent form. If you decide to leave the study early, the staff will talk with you about your treatment options.

Lactose: [The risks related to lactose ingestion include: upset stomach, abdominal bloating/cramping, gass and diarrhea.

What do I need to know about reproductive health and/or sexual activity if I am in the study?

Lovastatin risks to unborn babies are not well understood and there may be harm to a fetus in ways that are unknown. These risks may be a minor inconvenience or may be so severe as to cause death to a fetus. You should not be, or become, pregnant or breastfeed while on this research study. If you are sexually active, both men and women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectables, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable but least effective methods of birth control include male condoms (with or without spermicide) and female condoms. If you become pregnant or think

you may be pregnant at any time during the study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study; however, other treatment options will be discussed with you at that time if necessary

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any extra costs to you over that you would incur with the standard treatment for ISSNHL. The study will provide the lovastatin or the placebo at no cost to you.

All other drugs, tests and procedures are those that are standard for the treatment of ISSNHL. You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB (Institutional Review Board) and other representatives of this institution.

An exception to our promise of confidentiality is when we in good faith are permitted by law or policy to report evidence of elder abuse or neglect.

The sponsor(s), Department of Defense (DoD), monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), and the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?

The study doctor may need to take you off the study early without your permission if:

- The doctor thinks it is in your best interest
- The study is cancelled
- You are not able to attend the study visits as required by the study

The study doctor may also need to take you off the study drug without your permission if:

- You are not able to take the study drug as required by the study
- Continuing the study drug may be harmful to you

- You need a treatment that you may not take while on the study
- You become pregnant

What else do I need to know?

If you become ill or are injured as a result of this study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

You will be given up to 4 vouchers to pay for parking at the Northwestern parking lots near the hospital. On the first study visit, you will receive a $10 Starbucks gift card to be used while awaiting delivery of your study lovastatin or placebo. You may fill your methylpredisolone prescription at a pharmacy of your choosing. However, if you fill your prescription at any pharmacy and show it to the study coordinator when you receive your lovastatin or placebo, a $15 gift card to Walgreens or Amazon will be given to you. [For Walgreens card: Card can only be used for purchases of eligible merchandise at participating Walgreens or Duane Read locations in the United States, Puerto Rico and the US Virgin Islands or online at Walgreens.com. Eligible goods and services are subject to change in Walgreens sole discretion. Gift cards cannot be used to purchase other gift cards, prepaid open loop gift cards, third party gift cards, open loop prepaid cards/banking products or other financial services including but not limited to FedEX, Transit, Remittance, Virtual Banking products and Stamps. Cards cannot be reloaded, resold, used for payment outside of Walgreens, used for unauthorized advertising, marketing, sweepstakes, promotional or commercial purposes; redeemed for more than face value, transferred for value, redeemed for cash unless required by law, or otherwise prohibited by law. Gift card has no value until activated. Walgreens reserves the right to refuse to honor any gift card in the event of a disputed credit card charge, bounced check or other failure of consideration. For Amazon Card: Gift cards may only be redeemed toward the purchase of eligible goods and services provided by Amazon.com Services LLC and its affiliates on www.amazon.com or certain of its affiliated properties. Eligible goods and services are subject to change at Amazons sole discretion. Card cannot be used to purchase other gift cards, prepaid open loop cards, or certain third-party gift cards. Cards cannot be reloaded, resold, used for payment outside of amazon.com or affiliates, used for unauthorized advertising, marketing, sweepstakes, promotional or commercial purposes, redeemed for more than face value, transferred for value, redeemed for cash, returned for a cash refund, except to the extent required by law, or used in a manner otherwise prohibited by Amazon.com gift card restrictions and prohibited activity policy. Cannot be applied to purchase of goods or services at any amazon affiliated property outside of the United States.

The Accounting Services at Northwestern University will be given your name, address, and Social Security Number in order to issue a check for your study participation. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

HIPAA Authorization

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We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record pertaining to hearing loss
- Results of physical examinations
- Medical history
- Questionaires
- Records about study medication or drugs
- HIV testing results
- COVID 19 testing results
- Substance use
- Ethnicity

During this study, you may be coming to a Northwestern Memorial Healthcare Corporation entity for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to the Shirley Ryan AbilityLab (SRALAB) and Northwestern Memorial HealthCare/Northwestern Medicine entitities and its current and future affiliates.

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office]..

The following entities may receive your health information:

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.
- Clinical affiliates, including but not limited to the Shirley Ryan AbilityLab (SRALAB), Northwestern Memorial HealthCare, and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial may be

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tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.

- Clinical affiliates, including but not limited to Northwestern Memorial HealthCare, for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- The Department of Defense (DoD), who is sponsoring this study and its contractors and partners.
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).
- The study doctor must report positive HIV and COVID19 tests to the Illinois Department of Public Health (IDPH). The IDPH keeps track of all persons in the state with positive HIV tests. Information provided to IDPH include name, social security number, current address, telephone number, age, date of birth, age at diagnosis, race, ethnicity, sex, current gender, country of birth, residence at diagnosis and facility where diagnosis of HIV or AIDS was established.

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

Also, Federal law/42 CFR Part 2 prohibits unauthorized disclosure of these records.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will not expire.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to either of:

Donna Whitlon, PhD
Department: Otolaryngology
Address: 320 E. Superior Street
Searle Building; 12th floor; room 12-466
Chicago, IL 60611.

Alan Micco, MD
Institution: Northwestern Medicine
Department: Otolaryngology
Address: 675 N. St. Clair
Suite 15-200
Chicago, IL 60611

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You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent