STU00212929

PROTOCOL TITLE: Towards a Self-Administered Hearing Protection Regimen

(Short Title: Oral Statins and Hearing Loss)

PRINCIPAL INVESTIGATOR:

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	oral Lovastatin
IND / IDE / HDE #	N/A
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	100
Funding Source	Army CDMRP
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES

We have shown in guinea pigs and in mice that the HMG-CoA reductase inhibitor, fluvastatin, protects against noise induced hearing loss (NIHL) when delivered with osmotic pumps directly into the cochlea. Since the delivery of drugs directly into the cochlea is not a practical medical approach, we have used gavage (oral dosing) to deliver lovastatin to mice and have shown that this oral statin also protects against NIHL, although not as efficiently as direct delivery of fluvastatin.

Our approach to translate the finding into the clinic is to demonstrate that statins will also protect hearing in humans. Ethical concerns prohibit us from purposely exposing humans to sound levels that damage the cochlea, regardless of the magnitude of the hearing impairment it can generate. Alternatively, we have selected idiopathic sudden sensorineural hearing loss (ISSNHL) as our clinical target. ISSNHL is defined as a threshold elevation, initiated by an undefinable cause, of equal or more than 30 dB (relative to prior to the incident or relative to the opposite ear) at three consecutive frequencies of the human standard audiogram that occurred over a period of less than 72 hours (3 days). A comparison of work in the literature indicates that hearing loss initiated by different types of insult have multiple characteristics in common, and we have theorized that at least some of the mechanisms that underlie different types of hearing impairment overlap and can be addressed with similar drug therapies.

ISSNHL is typically treated with corticosteroids. Although the published outcomes after corticosteroid treatment often use non-standardized patient populations and measures, we estimate from the literature that even with prompt treatment, not all patients improve their hearing. In fact, approximately 30% of patients never regain any of their hearing in the affected ear. The available data on different forms of acquired hearing loss suggests that the study of statins in ISSNHL patients has the potential not only to improve treatment of ISSNHL but also to gain information that can be used to examine statins in other types of acquired hearing impairment.

This randomized, double-blind study is unique in the auditory literature. Ethically, for this initial clinical trial in which there is no definitive data linking statins to improvement of human hearing, we choose to work within the standard clinical practice guidelines for ISSNHL as applied routinely in Dr. Alan Micco’s otolaryngology clinic at Northwestern Medicine. On our protocol, all patients will receive the currently accepted standard drug protocol (oral methylprednisolone, with later intratympanic administration of dexamethasone (10mg/cc) as a salvage therapy, as required) given with visits over time that are predetermined in the clinical treatment. The only difference from the standard drug protocol is that the study patients will also be treated with a 7-day course of oral statin or oral placebo simultaneously with the methylprednisolone. All evaluation and testing will be as in the standard treatment, with no additional clinic visits.

Hypothesis

1. Statin, given in conjunction with oral methylprednisolone will improve outcome in ISSNHL patients over that in patients given oral methylprednisolone alone.

2. Patients receiving statin+methylprednisolone orally and who fail the initial 2 week hearing assessment, will do better on the intratympanic dexamethasone salvage therapy than those who received the oral methylprednisolone+ placebo.

3. Patients on every arm of the treatment initiated with oral statin + methylprednisolone will have a better tinnitus self-assessment than those who initially were treated with methylprednisolone placebo.

Specific Aim

Compare the effect of oral corticosteroid to corticosteroid+statin for ISSNHL by monitoring the recovery of hearing thresholds, speech discrimination and tinnitus self-assessment at each visit to the clinic during treatment of the hearing loss.

BACKGROUND

The following statistics are reported on the website of the National Institute on Deafness and Other Communication disorders (Updated December 15, 2016)

- About 15% of American adults (37.5 million) aged 18 and over report some trouble hearing.

- Roughly 10% of the US adult population, or about 25 million Americans, has experienced tinnitus lasting at least 5 minutes in the past year.

And according to the World Health Organization

- Over 5% of the world's population – or 466 million people – has disabling hearing loss.

At present, there are no drugs that are FDA approved for protection or repair of hearing.

Acquired hearing loss is hearing impairment that is not present at birth. Humans can suffer acquired hearing loss from a variety of physical and toxic insults that damage the inner ear. These causes include noise exposure as well as idiopathic sudden sensorineural hearing loss (ISSNHL), the subject of this study. ISSNHL is defined as a rapid (within 72 hours) onset of severe hearing loss of no known origin. The hearing loss is defined as a 30 dB threshold (the lowest sound level that can be detected) elevation at 3 consecutive frequencies of the standard audiogram. In the case of military personnel, in the performance of their jobs, they are exposed more often to high level noise which puts them at a higher risk for NIHL than those in the general population. It is because of this susceptibility the Army has funded this study. We have noted in a comparison of published work that acquired hearing loss induced by different types of insult have multiple pathologic and biochemical characteristics in common. We have theorized that at least some of the mechanisms that underlie different types of hearing impairment overlap and may be susceptible to similar types of drug interventions.

Treatment options to protect or repair hearing are few. Effort has focused on both technical and medical interventions, with limited success. As already underway in the military, acoustic engineering and design of new personal protective equipment can reduce the noise energy reaching the inner ear, but given the characteristics of military noises (jet engines, firearms, artillery, aircraft carriers), daily noise exposure can easily surpass the safe range. In the case of devices – hearing aids and cochlear implants – there have been improvements, but neither reinstates normal hearing and the use of these expensive interventions does not guarantee return to prior work life. At the edges of early medical research are cell regeneration and gene therapy approaches, which are presently far from their goal of reengineering a damaged cochlea and not yet medically viable. On the other hand, oral drug interventions to protect or repair hearing is an attractive option due to the possibility of attacking hearing loss by specifically targeting endogenous molecular pathways, limiting side effects, convenience, independent dosing and control, and potentially low cost. As stated above, there are currently no drugs that are FDA approved for protection or repair of hearing.

Physicians often prescribe what is considered the standard of care: off-label oral or intratympanic corticosteroids for sudden sensorineural hearing loss and sometimes noise induced hearing loss (NIHL), with only partial success. The facts remain that once hearing loss or auditory pathology occurs as a result of a variety of insults, there is little one can do except hope that the problem will spontaneously reverse itself, that steroids will reverse the problem, or that the use of hearing aids or cochlear implants will restore sufficient hearing for effective communication.

Systematic investigations for protective and curative drug interventions have been especially difficult because a full understanding of the pathological and molecular sequalae of any type of acquired hearing loss is presently lacking. In July 2020, clinicaltrials.gov listed only 6 drug intervention trials for SSNHL. Two were terminated, one is recruiting, 2 were completed with no posted results, and one that compared intratympanic to oral steroid showed no inferiority of IT steroid to oral. There was one additional study on NIHL that was withdrawn. There is a good reason why clinical trials for NIHL are nearly absent. The ethicality of causing a human hearing loss for scientific purposes, even a small temporary hearing loss, is controversial given the recent animal evidence showing that even noise that causes a temporary elevation in auditory brainstem response (ABR) thresholds can cause loss of hair cell/neuron synapses. On the other hand, trying to predict spontaneously occurring high level noise exposure in study subjects, or to carry out the very long-term studies needed to evaluate protection from chronic exposure is expensive, time consuming and usually inefficient, and is unlikely to ever be undertaken without a significant indication that the drug under consideration is promising for hearing loss. Moreover, studies using placebo alone as one arm of the trial are equally controversial, requiring the deprivation of standard treatment from some study subjects. Drugs in the pipeline that are also making their ways to hearing clinical trials may eventually be successful in obtaining FDA approval, but for various reasons (in addition to funding) for example unexpected toxicity, unpredicted off-target effects, drug availability or unexpected drug degradation, most will not.

Although full understanding of the molecular events driving hearing loss is lacking, a perusal of the literature leads us to theorize that regardless of the triggering event and initiating molecular responses that ultimately drive hearing loss, the ensuing cellular mechanisms eventually funnel into common molecular pathways. This can be inferred from both animal and (when available) human studies of NIHL, idiopathic sudden sensorineural hearing loss (ISSNHL), cisplatin and antibiotic induced hearing loss. Cochlear structure disruption has partial similarities in all four types of insults. In addition, treatments studied such as steroids, antioxidants, hyperbaric oxygen and c-Jun N-terminal kinase inhibitor show effects, albeit incomplete in multiple types. Mechanisms that support hearing are complex, and the drugs that will be effective in preventing or repairing damage will most likely be useful in combinations that focus on multiple mechanisms. Developing drugs for hearing loss is essential. The military, in particular, where the geographical location of hearing insult is not always immediately accessible by medical personnel, could use a drug(s) that could be safely taken independently at the time of insult, or, after future studies, prophylactically to protect hearing from noise induced and other cochlear pathology.

Statins for hearing loss. This clinical trial has its roots in our first *in vitro* experiments in which we invented a novel chemical screen for compounds that promote cochlear spiral ganglion nerve fiber regeneration *in vitro* using primary cultures of dissociated mouse spiral ganglia. The approach was novel because it allowed testing in actual auditory neurons rather than cell lines or other types of neurons. We reasoned that repurposing FDA approved drugs for hearing loss medicine would speed up the clinical use of the drug, avoiding extensive study of activities, side effects, off target activities, pharmacokinetics and toxicities in humans, since they are already mostly known in depth. Our blinded screen of a library of known drugs allowed us to identify HMG-CoA reductase inhibitor drugs (statins) as promoters of neurite elongation. Most, but not all statin drugs were active in the assay. The two most sensitive were cerivastatin and fluvastatin.

Although the statins were initially developed in order to slow the synthesis of cholesterol, the metabolic pathway divides into several arms, not all of them leading to cholesterol. Statins, by blocking the first enzyme in the pathway, cause depletion in metabolites in the different arms. By adding back a statin-depleted compound, geranylgeraniol (makes geranylgeranyl-PP) in a non-cholesterol arm, and showing that it blocked the neurite elongating effects of the statins, we demonstrated that spiral ganglion neurite elongation *in vitro* progresses through a non-cholesterol dependent arm of the HMG-CoA reductase pathway.

We chose fluvastatin for further evaluation in a NIHL guinea pig model, expecting to be able to destroy the hair cells with very loud noise (120 dB SPL x 4 hour x 4-8 kHz) and then to determine whether fluvastatin would stimulate disconnected neurites to regrow in the absence of hair cells. In the very first group of experiments, we delivered fluvastatin, initiated at the time of noise exposure, directly to the left cochlea through a cochleostomy via a catheter connected to a mini-osmotic pump for 30 days. Instead of being able to uniformly damage hearing by presumed loss of hair cells, unexpectedly in these experiments, fluvastatin protected both the operated cochlea as well as the contralateral cochlea (by a mechanism unknown at present) from the auditory brainstem

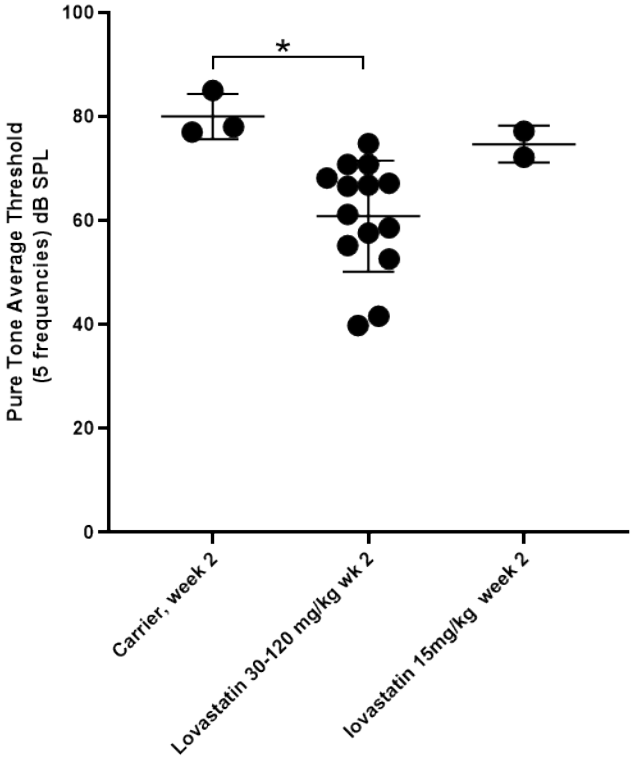
response (ABR) threshold elevation normally induced by high level noise exposure. This protection was associated with retention of inner and outer hair cells. In addition, the elevation of the number of retraction bulbs, a hallmark of neural degeneration, after noise exposure did not occur in the presence of fluvastatin. Moreover, promising for the development of drugs for hearing loss, in some of the guinea pigs (which are outbred animals) we observed protection from ABR threshold elevation even when the fluvastatin was initiated 1 week after exposure to noise.

Outbred animals may be good models for experiments in which a wide variation in genetic backgrounds is required. In fact, when we began with guinea pigs, we had no idea which or any genetic background would respond to fluvastatin. In our experiments, the inter-animal variation is high. We were lucky to see a significant response within such variation, indicating that the effect of Fluvastatin can be robust. However, in order to undertake mechanistic studies of fluvastatin, we moved to an inbred mouse model, CBA/CaJ, to be able to carry out experiments on a genetic background that was consistent across animals. Once again, we were fortunate that fluvastatin was effective on the first genetic background we investigated and we could show the protection at the earliest time measured, 1 week after noise exposure. Synapses were also protected from degradation in the fluvastatin treated mice. Fluvastatin, therefore, protects against high level noise induced hearing loss and concomitant degeneration of cellular structure in the cochleas in two different mammalian species.

Taken together with our observations, one can conclude that statins as a treatment for hearing loss is promising. In other regions of the nervous system, statins generally have a protective effect on neuronal survival and neurites. The protective mechanisms proposed vary, and include hypothesized up regulation of certain genes, regulation of non-cholesterol arms of the HMG-CoA reductase pathway, anti-oxidative, anti-immune, and anti-inflammatory functions.

Oral statins

Delivery of steroids directly to the cochlea is not a viable clinical approach, and we moved to evaluating oral delivery. One of the chief deterrents to development of new oral drugs for hearing loss is the unknown effects of the blood-labyrinth barrier, which regulates the passage of molecules from the blood into the cochlea. The blood-brain barrier, which is similar but not identical, does allow some oral statins to pass into the brain. Although there is very little known regarding statins as a treatment for hearing loss, three observations indicate that certain statins can cross the blood-labyrinth barrier. First, a study in mice with pravastatin reported protection against NIHL. Although that study used a noise insult of less power and likely less cochlear damage than in our own study, it did show protection of both temporary and permanent auditory brain stem response (ABR) threshold shift. Second, a recent report gave evidence that lovastatin delivered orally to mice could give a modest protection against hearing loss and cochlear damage due to cisplatin. Third, our recent work with lovastatin indicated a protection against hearing loss due to noise exposure. We calculated the pure tone average (PTA) of thresholds at 5 different frequencies: 4kHz, 8kHz, 12 kHz, 16 kHz, and 32 kHz. This is a similar approach to analyzing thresholds as seen in the clinic.



We found an average of >15 dB (p=.036) lower threshold in the animals treated with lovastatin (we combined all the active concentrations (30-120 mg/kg) for this graph) than those treated with the carrier alone. Since dB is a log scale, this is a significant difference and would be considered a significant improvement in the clinic. To do these studies, we chose just one timetable of statin delivery. We do not yet know if the response would improve with a different statin or a statin taken on a different timetable. Before undertaking this clinical trial, we will spend 6 months comparing different statin types at different concentrations in our mouse model to determine the most promising for the clinical trial. If they are all similar, we will use lovastatin. Taken together, these data suggest that stains likely cross-the blood-labyrinth barrier and protect against hearing loss initiated by at least two different insults.

Statins and auditory research in other laboratories. Outside of our laboratory, and those above, only a handful of other papers have considered statins in various aspects of hearing research. Experimental approaches and outcome measures differ, and the reports have been variable. *On the positive side*, simvastatin protects hair cells from gentamicin in culture; a statin protection from hearing loss was reported in apolipoprotein E knockout mice; a population-based survey suggested that statins may be beneficial for age-related hearing loss. *On the other hand*, simvastatin was reported to be toxic to spiral ganglion neurons in organotypic culture; a population-based study associated regular statin use (much longer than 7 days) and sudden sensorineural hearing loss; Simvastatin was toxic to cochlear neuroblasts and primary rat cochlear explants; and no effect of atorvastatin was found on development of hearing thresholds in sensorineural hearing loss in the elderly. Interestingly, three studies report trends or statistically small effects of statins on improvement of tinnitus. Taken together with our observations, although there is no real consistency, one might conclude that although there is no real consistency among different studies, statins as a treatment for hearing loss appears promising.

Methylprednisolone is a synthetic glucocorticoid whose key use in medicine is to interfere with inflammation and immune responses. Its use in hearing loss may also be due to these activities, but the exact mechanism(s) of action is not known. The function

of the drug in different cells depends on receptors, second messengers, and genetic expression that are specific to the cell being targeted. The broad effects of this corticosteroid on genes and pathways in different cells underlies its side effects, much of which are not entirely understood. For this reason, an alternate route of delivery of a different steroid, dexamethasone, intratympanic (IT), has been increasingly chosen either for primary treatment, for failed oral steroid treatment, or for those who are sensitive to corticosteroids. A study by Rauch showed that there was no inferiority of the IT treatment as compared to the systemic treatment in the therapy for sudden sensorineural hearing loss. Use of systemic and/or intratympanic steroid (both off label) has become the most widespread intervention for sudden sensorineural hearing loss.

Although the literature on the effectiveness of steroids is variable, their use (off label) in idiopathic sudden sensorineural hearing loss is recommended and is the standard of care for ISSNHL.

STUDY ENDPOINTS:

Primary study endpoints:

1) Improvement in pure tone averages of 15 dB or more; Improvement in speech discrimination.
2) Fewer patients whose pure tone averages and speech discrimination scores do not respond to treatment; More patients that respond fully or who have better partial response than with placebo.
3) Better outcome with the salvage therapy in patients who previously took the statin as compared to the placebo
4) Better self-assessment tinnitus scores in patients treated with statin as compared with those that took placebo.

Secondary study endpoints

1) No difference between males and females in outcome of those who took statin
2) No differences in outcome between those who arrive within 3 days of deafness onset and those who arrive after 2 weeks.
3) No differences in outcome between different age groups.

Primary safety endpoint

1) No worsening of hearing, speech discrimination or tinnitus in those who took statin.
2) None of the known statin side effects that are reported for long term statin use in patients who take the statin for 1 week.

STUDY INTERVENTION(S)/INVESTIGATIONAL AGENTS(S)

The drug under study is an FDA approved HMG-CoA reductase inhibitor called a statin. The initial plan is to use the FDA approved drug Lovastatin, 40 mg or placebo as an addition to oral methylprednisolone. Lovastatin was chosen based on preclinical data showing that atorvastatin, pravastatin and simvastatin do not protect against noise induced hearing loss as well as oral lovastatin. Oral methylprednisolone is the standard

of care for sudden sensorineural hearing loss as per the Clinical Practice Guidline:Sudden Hearing Loss; Otolaryngo Head Neck Surg (2019) 161 (1_suppl) S1-S45). It will be dosed in decreasing doses from 64mg to 11 mg over 11 days from the Medrol Pack as is standard of care in the Northwestern ENT clinic. When required, intratympanic steroid will be administered, approximately 1 cc of a concentration 10 mg/cc solution of dexamethasone. Lovastatin has been chosen after preclinical tests of atorvastatin, pravastatin, simvastatin did not protect against noise induced hearing loss as well as lovastatin in mouse. For lovastatin in humans, 40 mg is a moderate dose. Statins have been used in human medicine for decades for the purpose of managing cholesterol. However, since statins inhibit the first step in a biochemical pathway that has several arms in addition to cholesterol, statin can exert their functions through other mechanisms. The side effects of the statins are similar.

Lovastatin or placebo for the study will be prepared by the Investigational Drug Pharmacy at NMH so that the statin and the placebo look alike. The clinical coordinator or assistant will be responsible for interacting with the pharmacy and acquiring the drugs for the patient.

Subjects will be randomized by the IDS Pharmacy using a randomization table that has been developed by the pharmacy using the RPX program. After subjects are consented and found to be eligible for the study, they will be randomized to one of two groups with a separate table being used for female subjects (50 total, 25 drug and 25 placebo) and male subjects (50 total, 25 drug and 25 placebo).

The study capsules will be manufactured by the IDS pharmacy. Placebo capsules and matching active capsules will be prepared by re-encapsulating the active drug using the same empty gel capsules that will be used to prepare the placebo capsules. Lactose will be used as the filler for the placebo capsules and to supplement the active capsules.

Methylprednisolone (Medrol pack 16 mg tablets, tapering doses over 11 days, beginning with 64 mg/day and ending with 4 mg/day [2 days, 4 tablest; 2 days 3 tablets; 2 days 2 tablets, 2 days 1.5 tablets, 1 day 1 tablet, 1 day ½ tab, 1 day ¼ tab) and then dexamethasone IT, if required, will be prescribed by physicians in the ENT clinic. These steroids and their administration will be prescribed in the same way that these drugs would be prescribed to patients with ISSNHL as standard of care if they were not involved in this research. As both are FDA approved drugs and as they are being given as standard of care in the clinic, they do not require an IND exemption as used in this study.

Justification for IND exemptions for lovastatin (40 mg).

1. This drug is lawfully marketed in the USA.
2. The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
3. The research is not intended to support a significant change in the advertising for the product.
4. The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or

decreases the acceptability of the risks) associated with the use of the drug product.

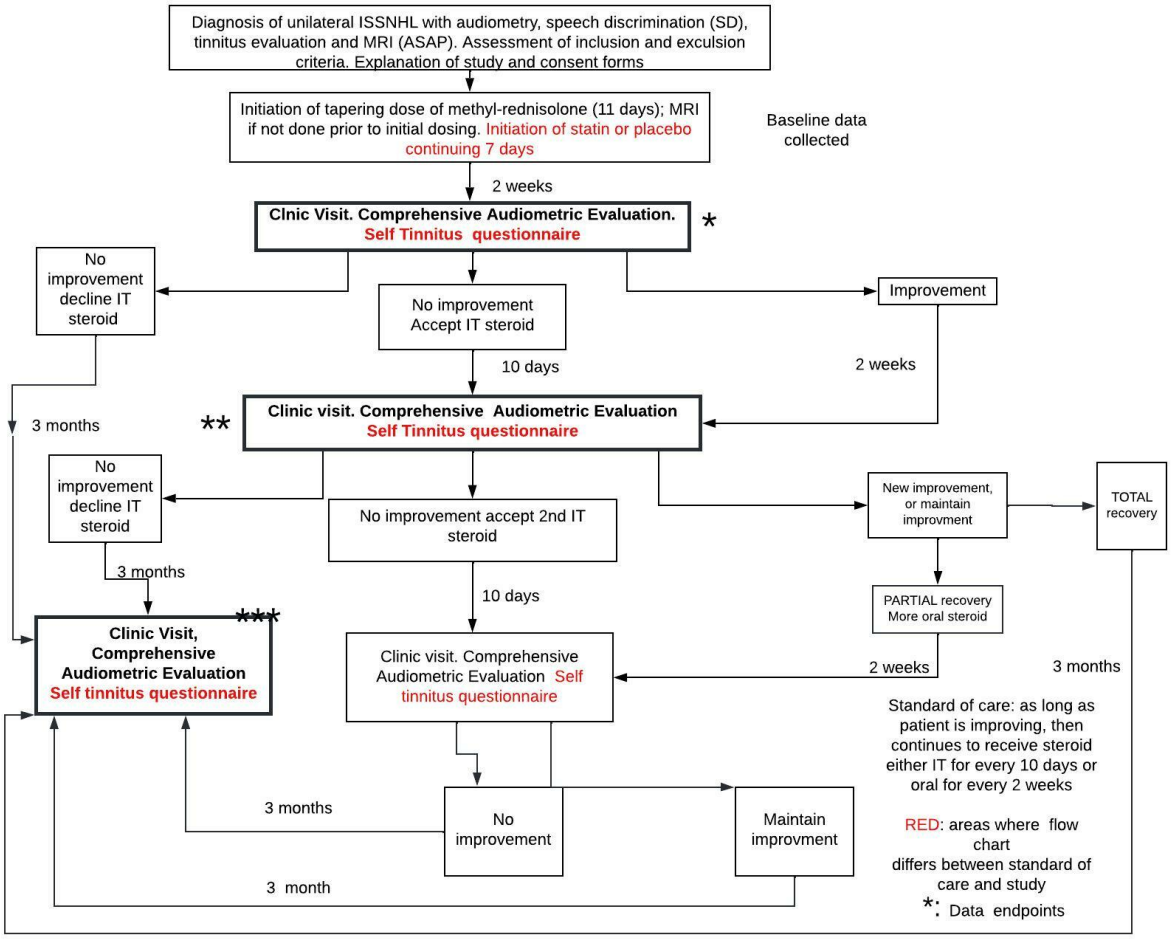
5, The research is conducted in compliance with the marketing limitations described in 21CFRS312

PROCEDURES INVOLVED:

Study design

This is a prospective, double blind, randomized study. After arrival in the clinic, initial determination of ISSNHL loss by a medical professional will use physical examination and patient history, (example: tuning fork, clinical observation of the ear canal and tympanic membranes, nystagmus, eye pain, redness, photophobia, headache, confusion, focal weakness, focal numbness, recent heard trauma, recent ear trauma, recent barotrauma), standard audiology and speech discrimination testing, evaluation of tinnitus to exclude contributing factors. All patients – study and non-study patients will undergo MRI to rule out retro-cochlear tumor, but the initial dosing will not wait for MRI results.

The approach for each patient is shown in the following flow chart:



Description of all research procedures

All study patients will receive the accepted treatment for ISSNHL – methylprednisolone on the standard timetable with the same scheduled visits depending on outcome. In addition to standard care for ISSNHL, which includes an 11-day tapering dose of methylprednisolone, study patients will receive a concomitant 7-day course of lovastatin or placebo. Subject to group assignments for each sex will be controlled by the randomized drug collection. Subjects will be coded and the code will only openly indicate male or female. Northwestern Investigational Drug Pharmacy will pre-package the drugs so that the placebo and statin cannot be visibly identified. Two sets of drug sets having 25 placebo and 25 statin doses of 7 pills in each will be prepared and randomized by the Pharmacy. One set will be for male patients. The other will be for female patients. When both sets have been given out, there will be equal numbers of males and females in the study and the recruitment for the clinical trial will end. The pharmacy will keep records of the drug assignments to specific coded subjects and will upload the records to the study folder kept on the FSM server. The patients, the MDs and other medical professionals will be blinded to the randomization of the drugs. The PI, Donna Whitlon, and the co-Investigator Claus Richter, who do not see the patients, will have access to all information as will the clinical coordinator.

Should a participant start the study but later be found by a delayed MRI to have abnormalities on the scan, that participant will be contacted and removed from the study.

Added risk to the standard treatment comes through the Lovastatin, 40 mg. FDA approved drugs that have been used over many years to lower serum cholesterol to the benefit of the patients. Methyl-prednisolone orally and dexamethasone Intratympanic (into the middle ear, IT) is a standard treatment for salvage of patients who do not respond to oral steroid. [Clinical **Practice** Guideline: **Sudden Hearing Loss** (Update). Chandrasekhar SS, Tsai Do BS, Schwartz SR, Bontempo LJ, Faucett EA, Finestone SA, Hollingsworth DB, Kelley DM, Kmucha ST, Moonis G, Poling GL, Roberts JK, Stachler RJ, Zeitler DM, Corrigan MD, Nnacheta LC, Satterfield L.Otolaryngol Head Neck Surg. 2019 Aug;161(1_suppl):S1-S45. doi: 10.1177/0194599819859885.PMID: 31369359]

The patient will be monitored during the treatment for side effects of the standard treatment as well as for known potential side effects of the statins. For severe side effects experienced by patients on the study, the patient will be instructed to stop taking the study drug, and to continue with the clinic visits and testing. The data from that patient will be retained.

Clinical data, hearing related relevant history and test results will be acquired from the patient electronic charts. Tinnitus self evaluations will be uploaded to the encripted desktop computer at the clinic which is backed up by Crashplan, and will be uploaded to the FSM server. Electronic binders will be created for each patient on RedCap. Information will also be didentified and added to each patient file.

Patients who improve are retreated with the steroid and asked to return in 2 weeks (oral) or 10 days (intratympanic) until there is no more improvement. Offering dexamethasone (10mg/ml) for salvage therapy follows the guidelines of the Clinical Practice Guidelines: Sudden Hearing loss update (doi: 10.1177/0194599819859885. The longest followup in this study will be approximately 4.5 months, depending on recovery. The number of clinic visits will depend on the response at each stage of the treatment (see above flow chart). For example, those with no response to oral drugs, no improvement after IT steroid, no improvement after second IT steroid, will have 4 visits after the intial diagnosis.

Study and nonstudy patients are treated identically except that the study patients receive 7 days of statin/placebo and are asked to complete the tinnitus evaluation at each clinic visit.

No Audio/Video Recording/Photography will be done.

DATA AND SPECIMEN BANKING

Consent forms will be stored in a locked cabinet in the clinic, uploaded to an encrypted computer (backed up by Crashplan) and onto the FSM server.

No specimens will be collected. Data from subjects will be anonymized by coding with an assigned number to each subject at entry into the study. Protected health information as required to provide care and as the hospital requires for its function will be retained together with the decoding key on an encrypted computer (backed up by Crashplan) in the clinic and on the FSM server.. All other clinical information, test results, information required for analysis of the results will be de-identified and only the deidentified data will be used in the analysis of the results. Only the clinical coordinator, the PI, Donna Whitlon and the Co-investigator, Claus-Peter Richter will have access to the PHI. After de-identifying the information, the subject's data are stored on the Clinic computer, the FSM server. De-identified data will also be stored on an encrypted password secured hard drive which can be accessed by the investigators named in this IRB.

The portable hard drive will be stored long term in a locked cabinet in the office of Dr. Whitlon in Northwestern Feinberg's Department of Otolaryngology.

SHARING RESULTS WITH PARTICIPANTS

Results of the test will not be shared with participants.

STUDY TIMELINES

Patients who have been diagnosed by a medical professional with one sided ISSNHL by physical examination, history, audiology, speech interpretation tests and tinnitus evaluation, who have been seen in the clinic within the first 2 weeks after the onset of symptoms, who meet the inclusion criteria and do not have any of the exclusion criteria will be considered for the trial.

Once enrolled the timeline of patient participation is the same as that of patients who are not on the study. The time line depends on the response to the treatments. See above Study Design Flow Chart. The longest participation will be approximately 4.5 months and will require 4 visits.

Individual, deidentified data will be calculated as it is acquired. Group data will be calculated at the end of the study when the code for treatment is broken.

Over 28 months of the clinical trial, we anticipate seeing about 370 ISSNHL patients in the clinic. From this we anticipate enrolling 100 patients, 50 males and 50 females.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

Patient older than 18 years and younger than 81 years, who are diagnosed with one sided idiopathic sudden sensorineural hearing loss by physical examination, history, audiology, speech interpretation tests and tinnitus evaluation, and who have been seen

in the clinic within the first 30 days after the onset of symptoms. Mean hearing threshold equal to or worse than >30 dB averaged across three consecutive frequencies.

Exclusion criteria

Children
Prisoners
Pregnant women, based on self-reporting
Women who are nursing, based on self-reporting

Patients with bacterial infections, mycoplasma, Lyme disease, tuberculosis, syphilis, fungal infections,
Autoimmune inner ear disease
Middle ear inflammation or effusion
Ototoxic medication such as chemotherapy, loop diuretics, high dose aspirin, etc.
Head Trauma, lead poisoning
Genetic disorders affecting hearing
Mitochondrial disorders, including MELAS (metabolic encephalopathy, lactic acidosis, and stroke-like episodes), stroke, Cogan's syndrome
Neoplastic (neurofibromatosis II, bilateral vestibular schwannomas, carcinomatous meningitis, intravascular lymphomatosis, others)*
Sarcoidosis
Hyperviscosity syndrome
Diabetes
Use of statins within the last 1 months
Allergy, hypersensitivity or intolerance to any components of the study medication

Prior otologic surgery other than ventilation tubes
History of drug abuse or alcoholism within the prior 2 years
Any psychiatric syndrome requiring treatment with neuroleptics, antidepressants, hypnotics or anxiolytics
Severe systemic neurologic disease (epilepsy, Parkinson's, dementia/Alzheimers, multiple sclerosis
Oral steroid treatment within the preceding 2 weeks
Heart disease or TIAs
Chronic kidney failure
HIV, Hepatitis B or C
Active shingles
Skull, facial or temporal bone anomalies
COVID-19 immunization within the last 30 days
Patients that medically cannot be treated with corticosteroids or statins or that the physician feels have possible coexisting problems that would cause participation in the study to be unsafe.

Note that because of delays in obtaining clinically related MRIs due to such issues as insurance clearance or appointment availability and because drugs to mitigate the ISSNHL need to be started immediately, subjects may be enrolled who subsequently

demonstrate MRI abnormalities that were not suspected at the time of referral for the study.In such a circumstance which are expected to be rare, the subjects will be contacted and told to stop the lovastatin.

Patients taking the following drugs: strong inhibitors of CYP3A4 , itraconazole, ketoconazole, Posaconazole, voriconazole, erythromycin and clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodine or cobicistat containing products; gemfibrozil, fibrates, lipid lowering doses of niacin (>1g/day), cyclosporin, danazol, diltiazem, dronedarone, verapamil, colchicine, ranolazine.

Patients who consume substantial quantitites of alcohol or who have a past history of liver disease. .

VULNERABLE POPULATIONS

Not included.

PARTICIPANT POPULATION(S)

The population of the city of Chicago proper is approximately 2.7 million. The Chicago metropolitan area comprises nearly 10 million. According to the U.S. Census Bureau the population by race at Chicago is 32.7% White, 30.5% Black or African American, 29% Hispanic, 6.2% Asian, 1.6% other (American Indian, two or more races, three or more races, Native Hawaiian Pacific Islander, and Native Hawaiian). Due to the small number of research subjects (100), no deliberate racial selection bias will be applied. The availability of subjects meeting the inclusion and exclusion criteria will be the selection determinants.

RECRUITMENT METHODS

When, where, and how potential participants will be recruited
Patients will be recruited from the patient base arriving at Northwestern Memorial Hospital for Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL).

Source of participants
Adults, eighteen to 80 are eligible for this study. Both genders will be eligible for the study and equal numbers will be assured by the drug assignment method. The study site, Northwestern Medicine, is located in a racially diverse high population area.

Describe the methods that will be used to identify potential participants
Patient between the ages of 18 and 80 who are diagnosed with one sided sudden sensorineural hearing loss by physical examination, history, audiology, speech interpretation tests and tinnitus evaluation, and who have been seen in the clinic within the first 13 days after the onset of symptoms will be further evaluated. If they meet the inclusion and exclusion criteria, they will be asked by the medical professional if they are interested in participating in a clinical trial. If yes, they will then meet with the clinical coordinator who will go over the inclusion and exclusion criteria, explain the study, and

go over the consent form and answer all questions. Because timeliness in initiating any treatment of SSNHL is essential, the patient can have only a short time – 1 hour- sign the consent form so that their standard therapy will not be jeopardized.

Materials that will be used to recruit participants

An information pamphlet will be used in the clinic areas. A page will be used on the Otolaryngology Web site to explain the study. Both are attached. These are mainly educational since there is only a short window of time between hearing loss and the end of the time limit (2 weeks) for recruitment. Most people do not realize how important it is to get immediate treatment. Therefore, foreknowledge will help them know what to do should sudden hearing loss happen to them and perhaps aid the study.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Patients will receive up to 4 coupons for parking in the hospital lots. A $10 gift card to Starbucks will be given to each participant to be used while they await delivery of the investigational drugs. A $15 gift card to Walgreens or Amazon will be given to patients who fill their steroid prescription by the end of the day and return to the clinic to show to the study coordinator, at the time when the lovastatin or placebo are given to the patient.

WITHDRAWAL OF PARTICIPANTS

Participants may withdraw from the study at any time.

The patient may cancel her/his consent and take herself/himself out of this study at any time with notice in writing to Dr. Micco or, Dr. Whitlon. Data that have been acquired by the time the patient cancels the consent will be retained and the patient will be asked for consent to continue acquiring information from the medical chart. Still all identifiable data will remain confidential. The patient will not be penalized for doing this. The patient's treatment by, and relations with Northwestern Medicine, its staff, now and in the future, will not be affected in any way if the patient does not want to take part in this study, or if the patient enters into the study and then withdraw from it.

If the patient withdraws from this study or choose not to participate, it will not affect their relationship with Northwestern Medicine or its clinical staff and the patient will continue to receive care as normal.

If the patient does not make the first clinic visit, or does not take the medication, the patient can be removed from the research without their consent. If the patient develops any severe side effect or disease, or becomes pregnant, the patient will be removed from the study.

RISKS TO PARTICIPANTS

Forseeable risks from the study are the same listed on the patient information sheet for statins:

In the case of the standard treatment of oral or intratympanic steroid, the risks are part of the typical treatment of ISSNHL and will be explained by the physician. In the standard treatment, methylprednisolone oral and dexamethasone, intra tympanic are given off label for ISSNHL and are the gold standard.

Lovastatin is an FDA approved drug that have been used for decades for the control of serum cholesterol. The dose, 40 mg, is a moderate dosage used for lowering cholesterol.

Additional risks in the clinical study procedures relate to the oral statin. Side effects of the drugs have been determined from long term use. There are no studies detailing use as short as 7 days.

The specifics from the Lovastatin drug insert are listed below but in particular, from studies of long term use.

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

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 co-administered 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 autoimmune 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 quantities of alcohol or who have a 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 been reported with HMG-CoA reductase inhibitors, including lovastatin.

Risks of Statins from studies of long-term use:

- Muscle problems. Statin use can rarely cause serious muscle problems that can lead to kidney problems, including kidney failure and rarely, death.
- Liver problems. Statin use can rarely cause liver problems that may rarely be serious.
- Diabetes mellitus. Increases in blood sugar have been observed in patients treated with statins. In some cases, these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes.
- Medical staff should be advised of:
    - 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
    - Passing brown or dark-colored urine
    - Feeling more tired than usual
    - Noticing the skin and whites of your eyes become yellow
    - Having stomach pain

Other problems that have been caused by long-term statins include headaches, rash (which rarely may be severe), severe allergic reaction or swelling, constipation, gas, diarrhea, pain or numbness in arms or legs, tendon rupture, urinary tract infection, dizziness, memory impairment and depression. All of these problems are uncommon to rare.

POTENTIAL BENEFITS TO PARTICIPANTS

We do not promise a benefit to participants. Since the study is aimed to determine whether statins improve recovery from ISSNHL, it is a possibility, but we do not know at this time.

DATA MANAGEMENT AND CONFIDENTIALITY

Data analysis plan

Patient numbers: We used the literature to estimate the number of patients for this study. Reported studies are highly variable with regard to definitions, measures, inclusion and exclusion criteria. Based on various reports, we estimate a SD in threshold elevation at the time of first measurement of ISSNHL hearing loss at about 25 dB. We have defined a significant difference in pure tone average thresholds between steroid and steroid+statin to be at least 15 dB. Using an online calculator http://statulator.com/SampleSize/ss2M.html), assumption of the power to be 0.8, alpha 0.05, the sample sizes of each arm are calculated to be 44 – total 88. We aim to recruit 100 patients to account for any withdrawal from an uncompleted protocol.

Descriptive statistics will be used. Means and quartile ranges will be calculated for each of the sets of data obtained from the patients. The data will be plotted accordingly. Moreover, averages and standard deviations will be calculated. Differences between the averages of the experimental groups will be tested with the analysis of variance (ANOVA). If the ANOVA indicated differences among the averages, a posteriori test will be used for making pair-wise comparisons among the averages. A significant difference

(HSD) test by Tukey will be used. The tests are part of a statistical package provided by IGOR® (Wavemetrics). Statistical decisions will be made for a probability with p=0.05. Dr. Richter and Dr. Dhar have experience with statistics and we will seek advice when needed from the statistics core.

Steps that will be taken to secure the data

Data will be de-identified by the study coordinator who will store the encrypted data, original and de-identified, on an encrypted computer backed up by Crashpad on an NMH/FSM approved e server behind the firewall. All data will be accessible to the coordinator, Drs Whitlon and Richter. All deidentified data will be assessable by any of the study participants. An encrypted, hard drive will store de-identified data for analysis and will be stored in a locked cabinet in Dr. Whitlon's Office.

Procedures that will be used for quality control of collected data

1. *Quality Control – Recorded Data*
    a. For handwritten information we will ensure that the handwriting is legible for all data collected.
    b. For personal information, the -study coordinator will make sure that birth dates, gender, and age are recorded correctly.
    c. Design a strict procedure for the random quality control of non-lab data recorded forms.
2. *Quality Assurance – Data Transfer*
    a. It is also possible to encounter errors when saving data to a hard drive. Data may not load correctly, so it is necessary to check that all data has been correctly saved.
    b. All paper data will be retained and stored in a locked cabinet
3. *Information which will be included in the data or associated with the specimens*
    a. Data files and specimen will be de-identified by replacing date of acquisition, name, gender and birthdate of the patient by a unique number. This allows correlating times and additional information to one patient but will not allow identification of the patient.
4. *Data or specimens storage*
    a. Data will be stored on a portable encrypted and password secured hard drive. Data are backed-up by an NMH/FSM approved data storage system.
5. *Duration for which data or specimens will be stored*
    a. Data will be stored for at least 10 years.
6. *Persons who will have access to the data or specimens*
    a. Only the study coordinator, the PI Dr. Whitlon and the Co Investigator, Dr. Richter, have access to the entire PHI information. Deidentified data will be used by the study investigators.
7. *Persons responsible for receipt or transmission of the data or specimens*
    a. Donna Whitlon is the person responsible for receipt of the data
8. *How data or specimens will be transported*
    a. Data will be saved and stored the FSM server. Dr. Whitlon will download the deidentified data onto an encrypted hard drive.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Overall safety will be monitored by a data safety monitoring board (DSMB). For each patient, the results of the hearing tests, speech discrimination tests and self-assessed tinnitus test will be recorded. After 33 patients of the 100 patients have been enrolled, the clinical coordinator will identify the data as coming from placebo or lovastatin treated patients. Any reported adverse reactions will be recorded with the data. The committee will use this data to determine a) if any adverse reaction is likely to have come from the use of the lovastatin and whether it is more than would be expected from treatment with lovastatin alone for other purposes as reported in the FDA drug brochure, the literature and/or from their experience; b) if the lovastatin interferes with improvement of hearing as compared to placebo. The committee will discuss whether or not any event is sufficient to pause the study for further consideration of next steps. Dr. Whitlon and Dr. Micco will meet with the two outside experts in order to clarify any questions they may have, but in order to avoid conflict of interest, only the two outside members will make the decisions. The results will be directly reported to the IRB. The committee will again meet after 66 patients have been enrolled. Outside members: Dr. Steven Rauch, Otolaryngology Harvard University, Massachusetts Eye and Ear Infirmary, Boston, MA. (Expertise in Sudden Sensorineural Hearing Loss);. Doctor Kurian Thomas, Director for Stroke Service, Stroke lead VISN 12, Jesse Brown VA, Chicago. (Neurologist, prescribes statins on a regular basis).

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

“Privacy interest”, a person’s desire to place limits on whom they interact or whom they provide personal information, is provided as the patient interacts mostly with his treating physician Dr. Micco or other medical personnel under his direction. Additional interactions are limited to the time of the patient with the study coordinator, who will also obtain informed consent.

The research team will receive the de-identified information through the study coordinator.

COMPENSATION FOR RESEARCH-RELATED INJURY AS IN THE CONSENT FORM:

If you need medical care because of taking part in this research study, contact the investigator and medical care will be made available. This care will be billed to you, your insurance or other third party.

Injuries sometimes happen in research even when no one is at fault. Northwestern University does not have a program for compensation. There are no plans to pay you or give you other compensation for an injury or adverse event, should one occur. However, you are not giving up any of your legal rights by signing this form.

ECONOMIC BURDEN TO PARTICIPANTS

There are no additional costs that participants may be responsible for because of participation in the research. Participants are treated and tested as with standard medical care.

Parking in downtown Chicago is expensive. We will arrange to give the participant a small financial offset for parking fees during the study.

CONSENT PROCESS

At the time of the clinic visit, and after identifying the patient as a possible candidate by Dr. Micco, the patient will be introduced to the study coordinator who will double-check the inclusion and exclusion criteria, explain the entire consent form documentation, and answer all questions. Written consent to participate in the research project will be sought and obtained directly from the participant at the clinic at the first visit to the clinic. To avoid misunderstanding due to language barriers, only English-speaking patients will be enrolled. No time restriction will apply during the consent process. It will be made sure that all questions and concerns of the participant have been addressed. Documentation will consist of a signed statement of informed consent approved for use by the Institutional Review Board (IRB). Participants will be informed of the tasks and time involved in the study. They will also be told that their participation is strictly voluntary and choosing not to participate will not harm their relationship with their clinical care providers in any way. They will also be informed that if they decide to participate, they can withdraw from the research project at any time, for any reason, and without penalty. Consent must be given within approximately 1 hour in order not to delay the standard treatment for ISSNHL

NON-ENGLISH SPEAKING PARTICIPANTS

Non–English speaking participants are not included in the study because one of the standard tests given to patients is the speech discrimination test, and it is given in English. In addition, it cannot be ensured that the oral and written information provided to non-English speaking participants will be in a language that they and we understand. Consent will be obtained in English.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

The study involves the creation, use, or disclosure of Protected Personal Health Information. HIPAA Authorization will be obtained from for all participants. The following information will be collected: all information in a medical record that can affect hearing loss; names; dates directly related to an individual, including birth dates, admission dates, discharge dates; Medical Record Numbers, Ethnicity

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

Feasibility of recruiting the required number of suitable participants within the agreed recruitment period and time devoted to conducting and completing the research.

Patients will be recruited from the patient base arriving at Northwestern Memorial Hospital for Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL). The medical billing codes (CPR codes) for right, left and bilateral sudden idiopathic hearing loss are H91.21, H91.22 and H91.23, respectively. Over the past 6 months the primary diagnosis was H91.21 in 33, H91.22 in 47, and H91.23 in 1 unique patient(s). From this data we estimate that over 28 months, 373 patients with unilateral idiopathic sudden sensorineural hearing loss will be seen at our clinic and provide sufficient patient numbers to recruit 100 participants.

Facilities and availability of medical or psychological resources that participants might need as a result of an anticipated consequences of the human research.

The Department of Otolaryngology - Head and Neck Surgery consists of Neurotologists trained in the latest medical and surgical management and treatment of various head and neck diseases and disorders-particularly the ear, nose and throat. Renowned for the treatment of head and neck cancer, the clinic at the Department of Otolaryngology at Northwestern Memorial Hospital (NMH) offers a multidisciplinary team approach to this disease process. It also offers advanced therapies for hearing loss, including conventional and programmable hearing aids and cochlear implants. Comprehensive diagnostic evaluations and state of the art, as well as standard treatment methods for a broad range of ENT problems are available.

Process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Dr. Whitlon and Dr. Micco will be responsible for ensuring that all the persons assisting with the research are fully informed about the project and procedures. Specific forms will be developed to ensure that at each meeting the proper information is acquired and recorded. Dr. Micco, will oversee the medical personnel and ensure that only the clinical coordinator or assistant acquires consent from the patients enrolled in the study. All will follow the flow chart as provided above by the PI, Dr. Whitlon, outlining the information to be gathered and examinations to be conducted.

MULTI-SITE RESEARCH

This is a single site study.