MANUAL OF PROCEDURES

Revised June 2008

Sudden Hearing Loss Multicenter Treatment Trial

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CHAPTER 1
STUDY OVERVIEW

1.1 SPECIFIC AIMS

Idiopathic sudden sensorineural hearing loss (SSNHL) is a common otologic emergency. Proposed etiologies include viral cochleitis, vascular compromise/ischemia of the inner ear, autoimmune inflammation, and inner ear membrane rupture. Despite thousands of publications on the topic, there have only been 13 English language randomized controlled trials of primary therapy for SSNHL. In the United States, there is consensus that minimum acceptable care should consist of a short (≤4 wk) course of oral corticosteroids. There is neither consensus nor good scientific evidence to support the addition of other treatments such as carbogen inhalation, antiviral drugs, volume expanders, or anticoagulants. Several publications have reported small case series of SSNHL in which intratympanic (IT) corticosteroid achieved a 50% success of salvaging hearing in cases of primary oral steroid failure, suggesting that IT corticosteroids may be as good or better than oral treatment. These studies have sparked widespread interest in this mode of drug delivery especially since intratympanic gentamicin for Meniere's disease has become one of the established, if not preferred, methods of treatment. If in fact IT steroids are shown to not be inferior, one explanation might be that the localized effect of a high inner ear drug concentration is sufficient treatment and systemic (oral) administration does not confer additional benefit. The present study is designed to resolve the question of whether IT corticosteroid is not inferior to systemic treatment for SSNHL. Herein we propose to compare the efficacy of oral vs. IT steroid therapy for primary treatment of SSNHL.

Specifically, we will:

1) Test the primary hypothesis that IT corticosteroids are not inferior to oral steroids for treatment of SSNHL. We propose to treat SSNHL participants presenting with ≥50 dB PTA in the affected ear in a randomized clinical trial (RCT) of oral prednisone vs. IT methylprednisolone. Participants will be randomized into two cohorts: one group will receive a 19-day tapering course of oral prednisone and the other group will receive IT methylprednisolone twice weekly for two weeks. Treatment efficacy will be assessed by pure tone and speech audiometry before and after therapy. Less than a 10 dB difference between the oral and IT arms supports the primary hypothesis that IT steroid therapy is not inferior to oral steroid therapy. Better outcomes in the oral treatment cohort will refute the hypothesis.
2) Compare the side effects and adverse events in participants treated with oral or IT steroids. There are no known local otologic adverse effects of oral (systemic) corticosteroid administration. Systemic side effects from a two-week tapering course of prednisone are likely to be small but non-trivial. IT steroids should avoid risk of any systemic side effects but have the possibility of causing local (otologic) adverse effects, such as further hearing loss, pain, or ear drum perforation. We will tabulate and compare the frequency and severity of such side effects in the two treatment cohorts.

SSNHL has been a well-known clinical entity for almost 60 years but there are still many controversies regarding the best treatment. Animal studies have shown favorable pharmacokinetics of IT steroid administration and IT steroid treatment has appeared promising in uncontrolled case series of SSNHL participants. However, IT treatment has not yet been subjected to randomized clinical trials. Despite the lack of rigorous trials, IT steroid use for SSNHL is spreading rapidly in clinical practice. This is reflected in courses taught on IT steroid treatment technique at the annual meeting of the American Academy of Otolaryngology – Head and Neck Surgery. This proposed

multicenter prospective randomized clinical trial will determine whether IT steroids are not inferior to oral steroids as primary treatment to restore hearing in SSNHL. This, in turn, will provide the basis for practitioners to make evidence-based treatment decisions in SSNHL. Thus, the results of this study are expected to have a high impact on clinical practice.

1.2 SIGNIFICANCE

Idiopathic SSNHL is a common otologic emergency first described in 1944 [1]. It is characterized by new onset unilateral hearing loss that develops within 72 hours. In some cases the patient feels a "pop" or senses the sudden onset of tinnitus and the hearing drops precipitously; in some cases the hearing drops over a few minutes or few hours; in others the patients awaken in the morning with the hearing loss. Some patients report hearing fluctuations or transient drops for days before the final loss occurs. There is virtually always some degree of associated aural fullness and tinnitus and varying degrees of imbalance or vertigo. Because aural fullness is such a common sensation, patients often delay for days or weeks before seeking medical attention. However this indeed constitutes a medical emergency as the window of opportunity for treatment is narrow and studies have shown that early administration of high dose prednisone is more efficacious than watchful waiting [2]. Audiometry confirms a unilateral sensorineural hearing loss. Loss of hearing in one ear leaves patients unable to localize sounds and makes it difficult to discriminate voices in noise. If left untreated, a minority of cases will show some degree of spontaneous hearing improvement in the first two to four weeks after onset. Hearing rarely improves thereafter. However, prompt administration of oral corticosteroids has been shown to increase the rate of hearing improvement from about 30% of cases to about 60% of cases [2]. It is unclear whether the incomplete response to oral steroid therapy is due to a significant amount of irreversible inner ear pathology or due to inadequate treatment. In the last three years a number of uncontrolled case series have been published reporting that intratympanic (IT) steroid injections can achieve a significant rate of hearing improvement in SSNHL cases that failed to recover with primary oral steroid therapy, even up to six weeks after onset of deafness. These observations support the notion that the current standard treatment with a short course of oral steroids is inadequate for maximizing hearing recovery. Furthermore, they suggest that local steroid delivery may have better efficacy than systemic administration. It cannot be determined from these uncontrolled case series whether IT steroids are not inferior to oral steroids or whether they are beneficial to a different (but overlapping) cohort of SSNHL patients. Despite the lack of prospective controlled trials of IT steroid therapy, this treatment is rapidly being adopted by clinicians who are seeking some means of obtaining further hearing improvement in SSNHL. The research project described herein is a multicenter prospective randomized clinical trial comparing the efficacy and risk of oral steroid treatment to IT steroid injections for primary treatment of idiopathic SSNHL. The results of this study will help resolve the question of best treatment in SSNHL. This, in turn, will shed light on basic pathophysiology and pharmacokinetics of the inner ear. The results will also provide the scientific basis for practitioners to comply with best "evidence-based medicine" decision-making standards for treating SSNHL.

1.2.1 Natural History and Etiology of SSNHL

Idiopathic SSNHL, the onset of unexplained unilateral sensorineural hearing loss (SNHL) in less than 72 hours, has an estimated incidence between five and 20 per 100,000 persons per year [3]. This is approximately the same incidence as Meniere's syndrome (15 per 100,000), an order of magnitude more common than acoustic neuroma (1 per 100,000), and about one-fifth the incidence of head and neck cancer (75 per 100,000) [NIH-NIDCD

Health Information website]. Simmons has speculated that incidence is likely underestimated as many who recover quickly will never seek medical attention [4]. Allowing for the limitations of retrospective methodology, there are a number of large case series from which to glean some basic epidemiologic features of SSNHL, and which, if taken cumulatively, account for approximately 7,500 cases in the United States, Europe, and Japan [3, 5-13]. The average age of affected individuals in these studies was 43-53 years. There was equal sex distribution. Vestibular symptoms were present in 28-57% of patients. Several series indicated a worse hearing prognosis with presence of vestibular dysfunction and/or with advancing age. All reports describing treatments indicated that earlier initiation of treatment was associated with better hearing outcome. In a retrospective tabulation of 28 untreated SSNHL patients, Mattox and Simmons noted that 22 (79%) showed at least some degree of spontaneous hearing improvement, although only 10 (36%) showed complete recovery. The prospective double-blind randomized controlled trial of Wilson et al. observed an overall 32% hearing improvement rate in placebo-treated patients [2]. Further analysis of their data indicated that the likelihood of recovery with placebo or no treatment was correlated with the shape of the audiogram: losses of less than 40 dB PTA or with mid-frequency loss up to 85 dB all had full hearing recovery, 40-50% of those with 40-90 dB hearing loss showed some spontaneous recovery, and only 24% of those with hearing worse than 90 dB showed any degree of spontaneous recovery. None of those with hearing worse than 90 dB had full recovery.

Not all cases of sudden deafness are idiopathic. Hughes et al. tabulated a "partial list" of causes of SSNHL [14]. They list 55 different infectious, traumatic, neoplastic, immunologic, toxic, circulatory, neurologic, metabolic, and other etiologies from the literature. "Idiopathic SSNHL" is the assigned diagnosis when no clear etiology is known. Although many mechanisms have been proposed, the most popular theories to explain these cases invoke viral or vascular etiologies. In fact, both of these mechanisms probably do occur. However, evidence supporting these theories is circumstantial.

There are four types of direct and indirect evidence for the viral theory of SSNHL: (1) temporal association of SSNHL with active viral upper respiratory illness, (2) serologic evidence of active virus infection, (3) histopathologic examination of postmortem human temporal bones, and (4) animal experiments demonstrating virus penetration of the inner ear. A number of authors have reported antecedent upper respiratory illness in 25-40% of SSNHL patients [6, 15-17]. However, these reports lack corresponding data on the prevalence of upper respiratory illness in a matched control population. There are numerous case reports of acute and convalescent antibody titers against herpes simplex type 1 (HSV-1), herpes varicella-zoster (HV-Z), cytomegalovirus (CMV), influenza A3, influenza B, parainfluenza B, rubeola, mumps, and rubella [18-20]. In 24 of 49 SSNHL cases with elevated viral antibody titers, Veltri et al. showed immunoreactivity against more than one virus [18]. Human temporal bone histopathologic studies have shown atrophy of the organ of Corti, spiral ganglion, and tectorial membrane; unraveling of myelin; and relative preservation of spiral ganglion cells [21, 22]. These findings are consistent with those observed in cases of presumed viral deafness. Guinea pig models of systemic viral infection [23] and CMV viral labyrinthitis [24] have shown viral particles in the spiral ganglion and demonstrated inflammatory reactions confirming inner ear viral penetration.

Three types of circumstantial evidence support the vascular theory of SSNHL: (1) sudden onset suggestive of infarction, (2) case reports of sudden deafness in association with known

systemic vascular diseases, and (3) histopathologic demonstration of cochlear changes due to vascular occlusion in animal models. The instantaneous onset of deafness in many cases of SSNHL is reminiscent of the onset of neurological events such as transient ischemic attacks or strokes that arise from thrombotic, embolic or vasospastic mechanisms. Perlman et al. demonstrated that labyrinthine artery occlusion in the guinea pig led to loss of cochlear microphonic after 60 seconds of anoxia and permanently depressed cochlear potentials after 30 minutes of anoxia [25]. Sudden deafness has been reported in cases of Buerger's disease, macroglobulinemia, sickle cell disease, fat embolism, and hypercoagulability [3]. These cases are all presumably due to hemorrhage, thrombosis, embolism or hypercoagulability. Histopathologic examination of guinea pig temporal bones after labyrinthine venous or arterial occlusion shows loss of spiral ganglion cells, mild or moderate damage to the organ of Corti, fibrosis of the cochlear duct, and eventual new bone formation within the cochlear duct (labyrinthitis ossificans). However, human temporal bone studies of SSNHL have not demonstrated labyrinthine ossification, the hallmark of labyrinthine ischemia [21,22]. Furthermore, the main cochlear artery runs from base to apex of the cochlea, creating the greatest risk of irrevocable hearing loss in the cochlear apex and affecting low frequency hearing. This prediction is opposite to clinical reports showing that low frequency SSNHL is the most likely to make spontaneous recovery or respond well to therapy. Finally, if the labyrinthine artery itself were thrombosed or spastic, both auditory and vestibular function should be impaired, but a minority of patients with SSNHL suffers dizziness.

1.2.2 Treatment of SSNHL

1.2.2.1 Primary therapy

Despite literally thousands of publications on the topic of SSNHL, a PubMed search from 1966–2002 yielded only 13 studies indexed as English language randomized controlled trials of primary therapy [2, 10, 26-36]. The many uncontrolled trials, retrospective reviews, and case series offer a multitude of different treatments. In each instance the justification for the therapy is based upon a presumptive etiology and physician preference. As noted above, the two most popular theories are viral and vascular. However, other mechanisms have been suggested including autoimmune mechanisms and metabolic disturbances. Virtually all published treatments, including so-called "shotgun therapy" of multiple simultaneous treatments achieve success rates of 40-75% in uncontrolled trials. In such uncontrolled trials there is no appropriate way to judge statistical significance, no effort to define an adequate sample size, no randomization of treatment assignment, no control or standardization of timing for treatment initiation, and a high likelihood of overestimating treatment effect. It is therefore prudent to discount this entire body of literature and focus on the small number of studies adhering to more stringent methodologic standards.

Most of the SSNHL treatments studied in randomized controlled trials can be divided into three different categories: (1) corticosteroid treatment, (2) specific antiviral therapy, and (3) specific treatment of vascular insufficiency. The justification for steroid treatment is based upon a presumed inflammatory process within the inner ear. Such inflammation might arise from a viral infection, an autoimmune mechanism, or even as a sequel of autolytic changes surrounding an area of ischemia or infarction. In other words, steroid therapy is nonspecific and may be beneficial in cases of differing etiologies. Antiviral therapy specifically addresses the viral theory of SSNHL.

Treatment of putative vascular insufficiency has been attempted with anticoagulants, volume expanders, vasodilators, and reduction of blood viscosity.

The first and most often cited randomized controlled trial of SSNHL therapy was by Wilson et al. [2]. In this trial 67 SSNHL patients at two clinical sites were randomized to receive oral steroids or placebo. Each of the two clinical sites used its own steroid protocol; one used a 12-day tapering course of oral methylprednisolone and the other used a 10-day tapering course of dexamethasone. Results from the two sites were pooled. A third cohort comprised 52 patients who refused to enter into the randomized study or could not take steroids and were followed as an untreated control group. Strict audiometric and temporal inclusion criteria and strict audiometric outcome measures were applied, conferring statistical power despite the relatively small sample size. Overall, 32% of the placebo group had hearing improvement, compared with 61% in the steroid group. Furthermore, there was a strong correlation between the pre-treatment audiogram and the outcome. Subjects with thresholds of ≤40 dB or mid-frequency ("U-shaped") losses of up to 85 dB invariably had excellent hearing recovery regardless of treatment assignment. Only 24% of subjects with flat losses of ≥90 dB showed any hearing improvement, and none recovered to normal. Subjects with 40-90 dB thresholds were in the "steroid effective zone", demonstrating a 38% recovery rate in the placebo group and a 78% recovery rate in the steroid-treated group. Across all subjects, the relative odds favoring recovery in the steroid group vs. the placebo group was 4.95:1; the relative odds favoring steroid treatment vs. untreated control was 4.06:1. The relative odds favoring untreated controls vs. placebo were only 1.22:1. The untreated controls and placebos were combined and the relative odds favoring recovery in the steroid-treated group was 4.39:1. While this is the best study to date showing efficacy of oral steroid therapy for SSNHL, the statistically significant treatment effect was only observed when data from two different treatment protocols were pooled and a clinically significant treatment effect may not have been achieved in many cases. Thus this study has been the basis for the widespread (though not universal) adoption of oral steroid therapy as the "gold standard" primary treatment for SSNHL.

There have been two randomized controlled trials of specific antiviral therapy. Stokroos et al. compared prednisone plus placebo to prednisone plus acyclovir in 44 SSNHL patients using a randomized, double-blinded protocol [31]. They demonstrated no additional benefit of adding acyclovir to the prednisone. Tucci et al. entered 105 participants into a randomized double-blinded comparison of oral prednisone plus placebo vs. oral prednisone plus valcyclovir [36]. As in the steroid study of Wilson et al. entry criteria, treatment assignment, and outcome measures were strictly defined and managed. Based on hearing tests at two-week and six-week follow-up, and an SF-12 symptom outcomes questionnaire, there was no significant difference between the two study cohorts. Both of these studies failed to show any benefit of adding antiviral drugs to oral steroids alone. It is unclear whether this outcome indicates that SSNHL is not viral, or simply that the timing or effective inner ear dosing of antiviral therapy was inappropriate.

Four randomized controlled trials have evaluated the efficacy of vasodilators as primary SSNHL therapy. In 1983, Fisch reported that inhalation of the CNS vasodilator carbogen yielded significantly better hearing outcome than the intravenous anti-vasospastic/volume expander combination of papaverine and dextran [26]. However,

subsequent studies of carbogen vs. anticoagulant therapy [10] and carbogen vs. steroid vs. placebo [34] failed to show any benefit of carbogen vasodilatation over placebo or other therapies. The study by Kallinen et al. suggested that anticoagulant therapy was somewhat more effective in patients with low frequency hearing loss and carbogen was better for patients with high frequency loss [10]. This may indicate that low and high frequency losses are due to different pathophysiologic mechanisms and therefore respond to different treatments. Mann et al. compared the calcium channel blocker nifedipine to their standard therapy of intravenous naftidrofuryl/vitamin A/vitamin E/zinc and found no difference between treatments [27]. In addition to Fisch's 1983 study, four other randomized controlled studies evaluated the efficacy of low molecular weight dextran, a volume expander used to improve circulation. Probst compared dextran plus pentoxifylline (a "rheologic agent" that reduces blood viscosity) vs. pentoxifylline alone vs. placebo [29]. Despite a study design providing 90% power to detect a 10 dB difference in treatment effect between groups, no significant difference was shown. Rosenberg et al. compared a procaine/dextran combination to placebo and found no difference between groups in a total sample of only 27 participants [28]. Suck full et al. found no difference between use of extracorporeal plasmapheresis to reduce serum cholesterol, fibrinogen, and lipoprotein in 18 patients to prednisolone/dextran/pentoxifylline treatment of nine patients [32]. Reisser and Weidauer randomized 72 patients to receive either pentoxifylline or ginkgo biloba extract [35]. There was no difference in hearing outcome between groups, although tinnitus reduction was better in the ginkgo cohort. Burschka et al. compared efficacy of two different dosages of ginkgo biloba extract in 96 SSNHL patients [33]. They observed high recovery rates in both groups, with a slightly better outcome in the higher dosage group. Finally, in a study by Sun et al. from People's Republic of China, 426 patients were randomized to receive an assortment of different treatments thought to affect iron metabolism [30]. The cohort receiving iron supplement had better hearing outcome than all other treatment combinations. These treatments are unconventional compared to those used widely in Europe and America. The theoretical basis for modulating iron metabolism is unclear.

Of the 13 randomized controlled trials of SSNHL treatment described above, only the one by Wilson et al. using oral steroids showed definite benefit for hearing recovery [2]. However, that study was designed to compare oral steroids to placebo, not to determine the optimum oral steroid regimen. There have been no randomized controlled trials published that compared different steroid dosing schemes to determine if one or another was better. However, recent uncontrolled trials of IT steroid have suggested that further hearing benefit may by obtained in some patients who fail to respond to conventional oral steroid therapy.

1.2.2.2 Intratympanic (IT) therapy in SSNHL

Conventional wisdom is that primary therapy of SSNHL is best achieved with oral steroids, that there is a "window of opportunity" during which steroids may be beneficial, and that there is little chance of hearing recovery after four weeks' duration of deafness or after completion of primary therapy. Recently, several publications have suggested that IT steroid administration can achieve higher inner ear drug concentration than the oral route and may be able to salvage hearing that does not respond to primary oral steroid therapy. Parnes et al. reported a two-part study in which they first used a

guinea pig model to compare the concentrations of hydrocortisone, dexamethasone, and methylprednisolone in plasma, endolymph, perilymph, and cerebrospinal fluid (CSF) when administered by oral, intravenous, or IT routes. They then used the results to design a treatment routine for IT steroid treatment in humans with a variety of inner ear disorders [37]. Their results in the guinea pig model can be broken into two parts, effects of administration route and effects of drug. For all drugs, oral dosing achieved equal levels of steroid in plasma, CSF, and perilymph. Intravenous administration caused a markedly higher drug level in plasma than other compartments. Intratympanic dosing yielded the highest inner ear drug levels, achieving equal concentrations in endolymph and perilymph. Of the three different steroid drugs, methylprednisolone produced the highest inner ear fluid concentrations for the longest time.

Dexamethasone, methylprednisolone, and hydrocortisone have relative anti-inflammatory potencies of 1:5.3:26.7 [37]. Taking into account these relative potencies, the variation in inner ear drug concentration, and the duration of drug in endolymph and perilymph, Parnes et al. concluded that IT methylprednisolone was the drug with the greatest potential for clinical application. They went on to administer IT dexamethasone or IT methylprednisolone to 37 patients with a variety of inner ear disorders. Of these, 13 had SSNHL. Only one had received any prior therapy. The other 12 had IT methylprednisolone as primary therapy. All presented within six weeks of SSNHL onset. Twelve patients received two to eight doses of steroid into the middle ear space by injection; one patient had bilateral relapsing disease and had a total of 29 doses. This last case did not behave like typical SSNHL and is omitted from the following analysis. Four of 12 were treated with dexamethasone, of whom two had full hearing recovery and two had no improvement. Eight of 12 were treated with methylprednisolone, of whom one achieved full recovery, three achieved partial recovery, and four had no change. Taken together, 3 of 12 (25%) had full recovery, 3 of 12 (25%) had partial recovery, and 6 of 12 (50%) had no response. The overall response rate to primary IT steroid therapy of 50% is equivalent to the results with oral steroids in other studies. It is notable that four of the IT responders had severely profound hearing loss outside of the “steroid responsive zone” defined by Wilson et al. [2] and therefore would be predicted to be unlikely to recover with standard oral therapy. The observation that IT administration could achieve equivalent or better hearing recovery than oral steroids while avoiding the risks of systemic administration makes IT steroid delivery an appealing treatment option. The high concentration and duration of methylprednisolone in the inner ear after IT administration raises the possibility that it might be effective in some cases which are refractory to oral steroids or in cases present longer than two to four weeks after onset.

Kopke et al. also studied IT methylprednisolone in a small number of SSNHL patients [38]. They administered methylprednisolone via an implanted middle ear microcatheter and continuous infusion pump for 14 days. They treated six patients, of whom four had SSNHL, presented within six weeks of onset, and failed a two-week trial of oral prednisone. They also treated three patients who initially presented more than six weeks after onset, one of whom had SSNHL. The patient who initiated primary IT therapy after six weeks had no hearing benefit. However, all four SSNHL patients who presented within six weeks and failed oral steroids showed hearing improvement from the IT therapy. Two had full recovery and two had partial recovery. Though the number of cases is extremely small, it is remarkable that 100% of patients who failed oral

steroids had hearing salvaged by two weeks of IT methylprednisolone treatment, even up to six weeks after onset of SSNHL.

Like Kopke et al., Lefebvre and Staecker used a continuous infusion pump to administer IT methylprednisolone to six patients who had failed to regain hearing using a six-day "shotgun" protocol of oral and intravenous corticosteroids, carbogen inhalation (central vasodilator), oral naftidrofuryl (vasodilator), diazepam (minor tranquilizer), and heparin (anticoagulant) [38,39]. All six patients received 10 µl/hr infusion of a 62.5 mg/ml methylprednisolone solution for ten days via catheter positioned adjacent to the round window. All six cases demonstrated 16.25-25 dB improvement in PTA and dramatic improvement in speech discrimination score.

In another uncontrolled study of IT therapy, Gianoli and Li treated 23 SSNHL patients with IT dexamethasone or methylprednisolone, 22 of whom had failed oral steroid therapy [40]. Ten patients (44%) achieved some degree of hearing improvement, although rarely to normal levels. There was a trend for better results in younger patients, men, and those treated with methylprednisolone. None of these trends was statistically significant. Unlike most other studies of SSNHL treatment, Gianoli and Li observed that the duration of deafness prior to initiation of steroid treatment did not significantly influence the hearing outcome. As in the studies by Parnes et al. [37], Kopke et al. [38], and Lefebvre and Staecker [39], there was evidence that IT steroid administration may be more effective than oral therapy. This increased efficacy may be in the form of an increased number of treatment responders, an increased proportion of full recoveries, or a lengthening the "window of opportunity" for initiating treatment. Taken together, these four studies are strongly suggestive that there is reversible inner ear damage that is not adequately treated by the levels of steroid that can be achieved by systemic oral administration but may be successfully treated by the higher inner ear drug concentrations achieved by local (IT) administration.

1.2.3 Summary

Idiopathic sudden sensorineural hearing loss is a common otologic emergency. If treated promptly, many patients can regain some hearing. However, the window of opportunity for treatment with oral steroids is usually less than four weeks. Oral steroid therapy has demonstrated efficacy in treating SSNHL, especially if the hearing loss is moderate to severe (40-90 dB). Severe-to-profound loss has only 25% chance of improvement with oral steroids. No other treatment has been shown effective in rigorous randomized controlled trials. Recent reports from multiple small uncontrolled series suggest that IT steroids (especially methylprednisolone) may not be inferior to oral steroids for treating SSNHL. Possibly, the higher concentration and duration of methylprednisolone in endolymph and perilymph after IT administration may be sufficient to obtain the observed treatment response. Furthermore, the IT route may achieve these benefits while avoiding the risks of systemic administration. These potential benefits of IT steroid treatment for SSNHL are exciting but unproven. They are based upon small case series without strict inclusion and exclusion criteria, randomized treatment assignment, or control groups. Herein we propose a multicenter prospective randomized controlled clinical trial comparing IT vs. oral steroid treatment in participants with idiopathic SSNHL.

While SSNHL is not one of the most common causes of deafness, it is disproportionately important because it is potentially reversible. Cases of reversible

sensorineural loss of various causes are natural experiments, offering investigators unique windows into basic physiology and pathophysiology of the inner ear. By studying SSNHL and its response to the proposed treatments we are likely to increase our knowledge about inner ear inflammation and its treatment.

One of the most frustrating experiences for clinical otologists is to see SSNHL patients who have delay in diagnosis that postpones initiation of steroid therapy. One potential benefit of the proposed study will be to highlight and publicize this disorder and its treatment. This study has purposely been designed to conform to the rigorous methodologic standards required for publication in a leading medical journal such as New England Journal of Medicine or JAMA where it can reach a much wider audience than can be achieved in a specialty (otolaryngology) journal. Raising awareness of SSNHL in the general medical community, the emergency medical community, and the public will lead to earlier otologic or audiologic evaluation and earlier diagnosis. This will undoubtedly lead to higher rates of treatment success.

We are in an era when evidence-based medicine is rapidly becoming the standard across all specialties. It is only through randomized controlled clinical trials of the type proposed here that we can generate the data upon which to base sound medical decision making. There have been thousands of publications on SSNHL but only 13 randomized controlled trials of SSNHL treatment. One of these demonstrated the unequivocal benefit of oral steroid treatment, and none defined the best treatment nor addressed the use of IT steroids. In the uncontrolled trials of IT therapy there has been an assumption that the side effect profile of this route of delivery is better than the oral route, but this assumption has not been tested either. Despite the absence of definitive studies about benefit and risk, IT steroid delivery is rapidly spreading as a treatment approach for a number of different inner ear diseases. Soon it will become entrenched even though scientific evidence of its efficacy is lacking. An example of this phenomenon is the recently completed clinical trial on autoimmune inner ear disease (AIED) conducted by many of the same investigators collaborating on this proposed SSNHL trial. Gradually, methotrexate had become established as the most widely used long-term treatment for AIED. However, based upon a five-year NIH-funded randomized, placebo-controlled clinical trial, methotrexate was proven to be no more effective than placebo in maintaining the hearing gains seen from prednisone alone [41]. This research proposal therefore comes at a critical time, when its outcome can have a powerful impact on clinical practice.

1.3. PRELIMINARY STUDIES

1.3.1. Coordinating Center Experience: Retrospective Review

The landmark randomized controlled trial of steroid therapy in SSNHL by Wilson et al. was conducted, in part, at the Massachusetts Eye and Ear Infirmary (MEEI) [2]. It established a tradition of prompt and consistent management of SSNHL patients, as well as a reputation that leads to a steady stream of regional referrals for assessment and management of SSNHL cases. We have reviewed retrospectively 10 years of SSNHL experience at MEEI from August, 1990 to March, 2001 [42]. Initial case retrieval was from the diagnostic coding records of the MEEI Otology Service, yielding 997 cases. After exclusion of incorrect coding, incomplete audiometric records, cases that did not meet our diagnostic and audiometric inclusion criteria, and cases where we could not adequately determine the type or timing of therapy, 318 cases were available for review. All of these patients experienced an idiopathic

unilateral SNHL that developed within 72 hours. They all had ≥25 dB hearing loss at three consecutive frequencies. They all had timely audiograms before and after steroid therapy. Steroid treatment was administered within one month of SSNHL onset in 266 of these cases and no treatment was administered in the remaining 52 cases. In order to better reflect the population of patients who most need hearing recovery and are least likely to get full recovery from primary oral steroids, we further constrained the analysis to those patients with ≥60 dB PTA in the affected ear. This constraint had the effect of eliminating patients who exclusively had low frequency or high frequency SSNHL, but retained those with significant mid-frequency losses. The exclusion of frequency extremes has two benefits: exclusion of low frequency SSNHL reduces ascertainment (misclassification) bias that might arise from mistakenly including patients with Meniere's syndrome, and exclusion of high frequency SSNHL lessens the likelihood of overestimating treatment benefit by including patients who might have threshold shift but no functional benefit to speech recognition. Thus the final analysis included 139 patients in the steroid-treated group and 22 in the untreated group. The hearing outcome is summarized in Table 1-1:

TABLE 1-1: Hearing Outcome in MEEI SSNHL Patients

Treatment (n)	Mean PTA improvement in dB (SD)	Final PTA <30 dB n (%)	Final WR ≥90% n (%)	PTA <30 dB AND WR ≥90% n (%)
Steroids (139)	28.0 (24.0)	35 (24.6)	27 (20.0)	22 (16.5)
No Steroids (22)	12.9 (23.0)	4 (18.2)	2 (9.5)	2 (9.5)

Final hearing with PTA of <30 dB and Word Recognition (WR) ≥90% was considered "Near-Normal Hearing;" i.e., too good to benefit from amplification with a hearing aid. Two important findings are apparent from these data: (1) SSNHL treated with oral steroids tends to have better outcome than untreated SSNHL, and (2) regardless of treatment, patients who present with ≥60 dB PTA SSNHL have only about 15% chance of regaining "Near-Normal Hearing."

1.3.2. Coordinating Center Experience: IT Methylprednisolone

Since November, 2001, 14 patients have been treated with IT methylprednisolone for SSNHL with ≥60 dB PTA. These patients were either oral steroid failures or had severe-to-profound SSNHL (≥90 dB PTA) and were therefore deemed unlikely to benefit from conventional oral steroid therapy. All began IT treatment within six weeks of SSNHL onset. Characteristics of these patients and their treatment outcomes are detailed in Table 1-2. All patients were informed that, although there are small published series of IT cases, this therapy is unproven. They all gave informed consent to try IT therapy. Treatment consisted of six injections, administered twice weekly for three weeks. The injections were directly through the tympanic membrane. Anesthesia was obtained with topical phenol solution painted directly on the tympanic membrane, a standard local anesthetic method for minor ear drum procedures. Usually this induced anesthesia of several weeks' duration and was only needed once or twice during the entire three-week treatment cycle. The treatment solution consisted of 0.1 ml of 2% lidocaine mixed with 1 ml of methylprednisolone sodium succinate (40 mg/ml). Approximately 0.5 ml was injected using a 1-ml syringe and 1.25-inch 25g needle. About half the patients experienced brief burning from instillation of the drug and one had transient vertigo lasting about an hour with his first two injections. Following injection, the patients remained supine with the head turned slightly toward the good side in order to sustain

immersion of the oval and round windows for 30 minutes. Patients maintained strict water precautions. Aside from transient burning and two episodes of transient vertigo, there were no adverse effects reported or observed. Although the injection site has a small perforation during the treatment cycle, no patient had persistent perforation at one month follow-up. Final hearing was tested one month after the last injection.

TABLE 1-2: IT Steroid Experience at MEEI

ID	Pre PTA	Post PTA	Pre WR	Post WR
DA	62.5	55.0	16	58*
TB	107.5	92.5	0	0
WB	72.5	58.8	22	12
GB	98.8	36.3	18	98*
BC	100.0	73.8	8	48*
DC	100.0	73.8	0	14
BF	85.0	81.3	12	6
JM	68.8	73.8	0	0
RN	111.3	63.8	0	34*
MO	112.3	75.0	0	42*
BR	112.5	26.3	20	100*
AW1	60.0	26.3	8	98*
AW2	105.0	21.3	0	97*
JZ	120.0	120.0	0	0
BZ	93.8	86.3	0	16*

Columns labeled "Pre" and "Post PTA", and "Pre" and "Post WR" indicate PTA and word recognition (WR) scores before and after IT treatment. An "" indicates statistically significant improvement in WR score. The mean improvement in PTA was 31.1 dB (s.d. 24.9). Significantly improved WR score was seen in 9 of 15 (60%).*

1.3.3. Data Management Center Experience: Hearing Studies

Data management of hearing test results is very complex compared with handling of other data commonly collected in clinical trials research. There are many data points generated in each audiogram or other hearing tests and these values must be tabulated with a high degree of reliability. The analyses of these data can be done many different ways. Clinicians and biostatisticians must work closely to develop and choose the appropriate statistical methods to perform the most meaningful analyses. The Data Management Center plays a critical role in preparing study results for publication. The Hines VA Cooperative Studies Program Coordinating Center (CSPCC) is the designated Data Management Center for this study. The CSPCC has served as the data center for two multicenter randomized clinical trials for hearing loss treatment. The results of both studies have been published in prominent journals [43, 44]. Dr. Reda (Principal Investigator [PI], Data Management Center) also participated in planning and writing the protocol for the NIH-NIDCD study of immunosuppressive therapy for AIED, serving as a biostatistician for the project during the design phase.

VA Cooperative Study #304 evaluated cochlear implants in subjects with profound hearing loss [43]. Eighty-two profoundly deaf subjects were randomly assigned to receive one

of three different cochlear implants. Twenty-four hearing tests were used to assess hearing preoperatively, and at 12 and 24 months postoperatively. The audiometric tests were grouped into five categories based on content, and a weighted composite index was developed to provide a single numerical indicator of the overall auditory response. The study demonstrated that multichannel implants are superior to single-channel implants, especially for understanding speech, that speech recognition improves over time, and that changes in speech processing strategies can improve patients' performance.

VA Cooperative Study #418 was a crossover trial comparing three types of hearing aid circuits [44]. This was a double-blind, three-period, three-treatment crossover trial conducted at eight participating Veterans Affairs medical centers. Three hundred sixty subjects with binaural SNHL were randomly assigned to one of six sequences of linear peak clipper, compression limiter, and wide dynamic range compressor hearing aid circuits. Main outcome measures included speech recognition, sound quality, and subjective hearing aid benefit compared at baseline and after each three-month intervention with and without a hearing aid. The study demonstrated that all three hearing aid circuits provided significant benefit compared to the unaided condition. Both compression limiter and wide dynamic range compressor circuits provided better listening experience than linear peak clipper circuits with respect to word recognition, loudness, overall liking, aversiveness of environmental sounds, and distortion. In rank order, participants preferred compression limiter more frequently than wide dynamic range compression, and wide dynamic range compression more frequently than peak limiter. The differences between aided groups were much less than the differences between aided vs. unaided conditions. A long-term follow-up substudy of the participants in Cooperative Study #418 is currently being conducted.

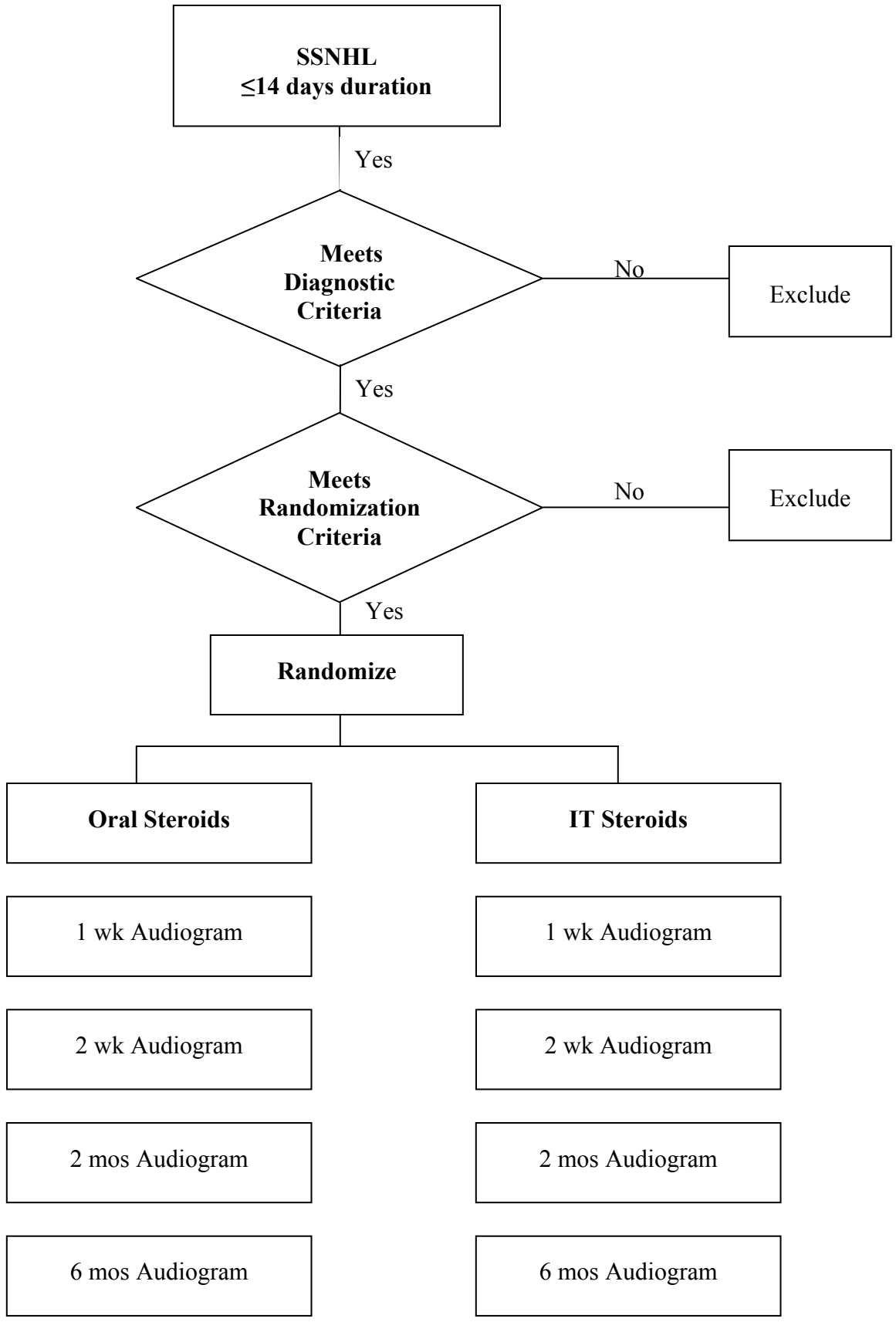
1.4 RESEARCH PLAN

1.4.1 Study Design

The Sudden Hearing Loss Multicenter Treatment Trial is a prospective randomized clinical trial consisting of a head-to-head comparison of oral prednisone and IT methylprednisolone sodium succinate (Solu-Medrol®) for primary treatment of idiopathic SSNHL. All consenting potential participants who meet enrollment criteria will be randomized to one of the two treatment arms. The oral prednisone arm will consist of a 14-day "burst and taper" regimen (60 mg/day for 14 days, followed by a five-day taper [one day each of 50 mg, 40 mg, 30 mg, 20 mg, 10 mg]) representing current standard care of SSNHL. The IT methylprednisolone arm will consist of four injections (twice weekly for two weeks) administered on an outpatient basis in participating otology clinics. Hearing will be tested and safety monitoring lab work obtained at one week, two weeks, two months, and six months after initiation of therapy (see Study Flowchart). Hearing outcome will be assessed by standard audiometric measures of pure tone audiometry and speech recognition. Secondary outcome measures will include assessments of discomfort and adverse events associated with each treatment.

Study participants will be enrolled at eight Clinical Sites: Massachusetts Eye and Ear Infirmary, Cleveland Clinic Lerner College of Medicine, Johns Hopkins University School of Medicine, New York University School of Medicine, University of California San Diego School of Medicine, University of Iowa Hospital and Clinics, University of Massachusetts Medical School, and University of Michigan Medical School. If necessary, additional sites will be added as the study progresses to provide sufficient sample size.

SSNHL Study Flowchart:



1.4.2 Rationale

The overall objective of this study is to compare the efficacy and risk of oral vs. IT corticosteroids for treatment of SSNHL patients. We hypothesize that hearing recovery from IT steroid treatment will not be inferior to that of standard oral steroid therapy. It is well-known that a minority of SSNHL patients get full recovery from primary oral steroid therapy, especially if the magnitude of the initial loss is large. Pilot studies have shown that some patients who failed to achieve recovery from oral steroids got further benefit from salvage IT therapy, suggesting that IT therapy may not be inferior to oral treatment. The head-to-head comparison of oral and IT therapy by the randomized clinical trial proposed herein will resolve this question. The proposed project is designed as a non-inferiority study. The slightly greater sample size requirements needed to test non-inferiority are offset by the fact that the hypothesis of non-inferiority is both more statistically appropriate and clinically applicable. Our secondary outcome measures of discomfort and adverse events associated with each treatment will provide important information about the overall impact on patients of receiving these therapies. If, as we hypothesize, IT is not inferior to oral, then the side effects and adverse events in each treatment arm will be critical information in making evidence-based clinical decisions. Thus the results of this study will have a substantial impact on clinical practice guidelines for SSNHL.

Several study design decisions have been made whose rationale will be discussed explicitly:

Audiometric Inclusion Criteria and Outcome Measures

The study will be limited to participants with no known antecedent hearing asymmetry. Since most potential participants presenting with SSNHL have not had a recent audiogram prior to onset of deafness, limiting the enrollment to participants with previously symmetric hearing will enable us to use the contralateral ear as an estimate of pre-SSNHL baseline.

Participants must have SSNHL of ≥50 dB PTA in the affected ear. The PTA of the four audiometric frequencies, 500, 1000, 2000, and 4000 Hz is a widely accepted summary measure of hearing. It obviously underrepresents threshold shift below 500 Hz or above 4000 Hz. However, threshold shift of these frequency extremes, though very noticeable to a patient, is unlikely to have measurable effect on speech reception or word recognition. In order to clearly demonstrate a difference in treatment effect between oral and IT steroids, pre-treatment hearing loss must be great enough to allow for significant hearing recovery. Our pilot data predict that a ≥50 dB PTA inclusion criterion will satisfy this requirement. Furthermore, this will focus the study on the population with the greatest clinical impact, those with loss of hearing in the speech frequencies and lowest likelihood of recovery by conventional treatment. Word recognition score will not be used as an inclusion criterion, but will be tested at enrollment and at follow-up as one of our audiometric outcome measures.

Dosage and Timing of Steroid Treatments

There is a wide range of oral steroid dosage in general use for SSNHL, from a six-day taper of oral methylprednisolone at the low end to four weeks of prednisone 80 mg/day at the high end. Our protocol calls for a prednisone dose of 60 mg/day for 14 days followed by a five-day taper (50 mg, 40 mg, 30 mg, 20 mg, and 10 mg). This falls in the middle of the dosage range in common usage and is an acceptable balance of steroid side effects vs. treatment benefit. Current practice makes use of standard ("one size fits all") prednisone

dosing for adult patients with SSNHL. There is no evidence to suggest that dosing by body weight improves efficacy or reduces risk in the relatively short taper proposed in this study. Furthermore, it is highly impractical to give oral prednisone in step sizes less than 5 mg.

The IT dosage for this study, twice weekly for two weeks, falls within the 10-21 day treatment protocols in published studies (see Background and Significance) [37-40]. It is also consistent with the pilot experience of the participating Clinical Sites. Furthermore, there is a methodologic advantage in having equal treatment duration in both treatment arms of the study in order to eliminate a potential confounding variable if treatment duration was unequal. The IT drug will be administered via direct injection through the tympanic membrane in order to avoid any confounding effect of having a ventilating tube in the IT-treated ears but not the oral prednisone-treated ears.

There is incontrovertible evidence that a "window of opportunity" exists for treating SSNHL. In order to compare efficacy of our two treatment arms, we will limit enrollment to potential participants presenting within 14 days of SSNHL onset. Ideally, the study should be restricted to participants who have received no SSNHL steroid treatment prior to enrollment and randomization. However, because there is substantial awareness of this condition in the general otolaryngology community and many potential participants may seek local otolaryngologic evaluation before presenting to the participating tertiary referral Clinical Sites, a subset of potential participants may have initiated oral steroid therapy before enrollment. As long as the total duration of steroid treatment is less than 10 days and they still meet audiometric entry criteria, we will enroll and randomize such participants. While we are hopeful that our proposed aggressive publicity/recruitment efforts will tend to identify untreated potential participants, we do not want to attenuate our potential pool of participants by excessively stringent enrollment criteria. Depending upon the proportion of enrolled participants with steroid treatment prior to randomization, data analysis may include a *post hoc* stratification on this factor to see if there is a trend suggesting that it is correlated with outcome.

Control Groups

This RCT is a Phase III trial of oral vs. IT corticosteroid. Thus, we are comparing an experimental treatment (IT steroid) to standard (oral) therapy to assess relative efficacy and safety. We cannot ethically assign participants to a "no treatment" arm. We gave consideration to a comparison of oral prednisone alone to oral prednisone *plus* IT methylprednisolone. However, this has some disadvantages. While such a study would have a theoretical option of allowing us to have an oral+IT placebo control group, we deem it improbable that participants would consent to IT placebo injections. If the oral+IT methylprednisolone cohort fared better than the oral only group we would still be unable to answer the question of whether oral steroids (with their attendant risks) are really necessary.

1.4.3 Study Objectives

The overall objective of the proposed research is to identify and quantitate the benefits and risks of oral vs. IT corticosteroids for primary treatment of idiopathic SSNHL. As part of this multicenter collaborative RCT, we plan to meet the following specific objectives:

1.4.3.1 Primary study objectives

The primary study objectives are:

1) To compare efficacy of oral prednisone vs. IT methylprednisolone as primary treatment of SSNHL by conducting a randomized prospective clinical trial in participants presenting within 14 days of SSNHL onset, and
2) To compare the relative risk of side effects and/or adverse events in the two treatment groups by documenting the major and minor adverse events and pain experienced by each study participant.

Explicit criteria for defining the SSNHL diagnosis, hearing loss severity, and hearing improvement are based on pure tone air conduction thresholds and word recognition scores collected during standardized audiometric tests (see Section 1.4.1, Primary Outcome Measure). The study design permits a one-tail evaluation; the experimental (IT) treatment can be shown to be no worse than standard (oral) therapy. The proposed RCT is designed to provide 90% statistical power for showing non-inferiority, if the average change in PTA for IT is no more than 10 dB less than the average change in PTA for oral (see Section 3.6.2, Hypothesized Treatment Effect). The null hypothesis being tested is that hearing improvement in the cohort of randomized participants receiving IT methyprednisolone is inferior to that in the cohort receiving oral prednisone treatment.

1.4.3.2 Secondary study objectives

The study will have the following secondary objectives:

1) To determine the proportion of participants with severe-to-profound SSNHL who achieve recovery to normal or near-normal hearing (≤30 dB PTA and ≥90% WRS) when treated primarily within two weeks of SSNHL onset; and
2) To describe the natural history of treated SSNHL during a six-month follow-up interval.

1.4.3.3 Subgroup Analyses

The SSNHL study will characterize any differences in the outcome measures and treatment effects among subgroups of participants based on race, gender, age, vestibular symptoms, duration of SSNHL prior to initiation of treatment, duration of pre-enrollment steroid treatment, and audiometric level at the time of enrollment. For quantitative variables, the median value will be used to define two subgroups. However, the study only has sufficient power for the overall comparison of the two treatment groups. Subgroup analyses will be considered exploratory rather than definitive.

1.4.3.4 Operational Objectives

The SSNHL study will have the following operational objectives:

1) To recruit, randomize, and follow for a total of six months a total of 254 participants across the participating Clinical Sites who will meet a specific set of inclusion/exclusion criteria;
2) To promote adherence to prescribed study regimens;
3) To maintain clinical well-being and proper participants safety; and

4) To monitor and maintain the precision and accuracy of the assessments of study measures.

1.4.4 Study Medications

The choice of the specific treatment interventions for primary treatment of SSNHL (oral prednisone or IT methylprednisolone sodium succinate) is based upon a careful assessment of risks and benefits of the study population. The proposed oral treatment is well within the range of corticosteroid dosage and duration considered standard care for SSNHL. There are published uncontrolled case series in the literature suggesting substantial potential benefit of IT methylprednisolone for primary SSNHL therapy or salvage of primary therapy failures. Reported side effects and complications in these series have been low. This study will use a dosing regimen within the range reported in these pilot series.

1.4.4.1 Prednisone

Prednisone is a corticosteroid that is produced naturally by the body and is important for maintaining good health. Prednisone is often used as part of treatment for a variety of different diseases such as severe allergies, arthritis, and respiratory and skin problems. Prednisone is also used for other conditions for its anti-inflammatory and immunosuppressive actions. Prednisone's mechanism of action as an immunosuppressant is not completely understood but may involve prevention or suppression of cell-mediated immunity, antibody-mediated reactions, and specific actions that affect the immune response. In the proposed study we will be using an oral preparation of this drug.

1.4.4.2 Methylprednisolone

Methylprednisolone has actions similar to prednisone. Unlike prednisone that must be metabolized in the liver to an active form, methylprednisolone is already able to bind to steroid receptor sites without further metabolic modifications. On a milligram-for-milligram basis, the relative dosing of prednisone:methylprednisolone is 5:4; that is, 5 mg of oral prednisone is equipotent to 4 mg of oral methylprednisolone. In the proposed study we will be using the injectable/intravenous preparation of methylprednisolone sodium succinate (Solu-Medrol®) in a concentration of 40 mg/ml.

1.4.5 Study Population

The participants in this study will meet the following inclusion criteria and be free of any condition that would constitute a systemic or otological exclusion criterion. Table 1-3 summarizes key selection criteria that define the study population.

1.4.5.1 Inclusion criteria

1) Males and females ≥18 years of age in good health
2) Unilateral SNHL developing within 72 hours
3) Pure tone average ≥50 dB based upon four frequencies (500, 1000, 2000, and 4000 Hz) in the affected ear, with the affected ear ≥30 dB worse than contralateral ear in at least one of the four PTA frequencies
4) To the best of the participant's knowledge, hearing prior to onset of the SSNHL was symmetric.
5) Hearing loss must be determined to be idiopathic following an evaluation by an otolaryngologist, appropriate blood tests, and imaging studies.

6) Participants may be enrolled if they have preexistent symmetric SNHL due to presbycusis or preexisting noise-induced hearing loss, provided that a new unilateral hearing loss meeting criteria 2 and 3 (above) is present.
7) Participant enrollment must be accomplished within 14 days of SSNHL onset.
8) Participants may be enrolled and randomized even if they have already begun oral steroid treatment for their SSNHL, as long as the total duration of oral steroid treatment is less than 10 days and an audiogram performed at the time of enrollment confirms that they meet all audiometric inclusion criteria. Once randomized, they will be treated as if no prior steroid treatment was administered.
9) Participants must be able to read or write English or Spanish. They must be able to repeat words in English or Spanish so that word identification tests can be conducted.

1.4.5.2 Exclusion criteria for systemic disease

The following conditions or situations would contraindicate entry into this study because there would be significant risk of ascertainment (misclassification) bias regarding the correct diagnosis of idiopathic SSNHL or because of significant risk from their disease if such participants were given immunosuppressive drugs. Whether or not the participant meets criteria will be determined by the PI at each site.

1) >21 days prior oral steroid treatment for any reason within the preceding 30 days or ≥10 days prior oral steroid treatment of SSNHL within the preceding 14 days
2) History of tuberculosis or of prophylactic tuberculosis therapy for positive skin test (PPD)
3) Insulin-dependent diabetes
4) History of rheumatic disease, including rheumatoid arthritis, scleroderma, lupus erythematosus, polymyalgia rheumatica, polyarteritis nodosa, temporal/giant cell arteritis, Sjögren's syndrome, or ulcerative colitis
5) History of unstable angina, coronary artery stenting or bypass grafting within three months of enrollment, transient ischemic attacks or stroke within four weeks of enrollment, or cardiac arrhythmia
6) Serious psychiatric disease or history of psychiatric reaction to corticosteroids
7) Prior treatment with chemotherapy agents, immunosuppressive drugs (azothioprine, cyclophosphamide, leukoran, or other alkylating agents), or cyclosporine, FK506, etanercept, infliximab, or interferon
8) Pancreatitis
9) Active peptic ulcer disease or history of gastrointestinal (GI) bleeding
10) History of known HIV, hepatitis C, or hepatitis B infection
11) Chronic renal insufficiency requiring dialysis
12) Alcohol abuse
13) Active shingles (herpes zoster infection)
14) Advanced/severe osteoporosis or nonsurgical (mild) aseptic necrosis of the hip
15) General anesthetic for any reason within two weeks of enrollment
16) History of head and/or neck radiation therapy

1.4.5.3 Exclusion criteria for otologic disease

The following conditions or situations would contraindicate entry into this study because of the significant possibility that they could cause SSNHL, resulting in ascertainment bias regarding the correct diagnosis of idiopathic SSNHL as defined herein.

1) History of previous or recurrent unilateral SSNHL
2) History of fluctuating hearing in either ear
3) History of Meniere's syndrome in either ear
4) History of chronic granulomatous or suppurative otitis media or cholesteatoma in either ear
5) History of otosclerosis in either ear
6) History of prior ear surgery of any kind (except ventilating tubes in childhood)
7) Asymmetric SNHL prior to onset of SSNHL
8) Any congenital hearing loss, even if symmetric or conductive
9) History of blunt or penetrating ear trauma, barotrauma, or acoustic trauma immediately preceding SSNHL
10) History of luetic deafness according to criteria outlined by Darmstadt and Harris [45]
11) History of genetic SNHL with strong family history
12) Craniofacial anomalies or known temporal bone malformations as revealed by CT scanning

TABLE 1-3: Study Participant Selection Criteria

Criteria	Mode of Ascertainment
≥18 years of age	Self report
Unilateral SNHL developing w/in 72hr	Self report
PTA ≥50 dB, affected ear ≥30 dB worse than contralateral side in at least one PTA frequency	Audiometry
Hearing symmetric prior to SSNHL onset	Self report
No other identifiable cause of SSNHL	Self report, history, evaluation by otolaryngologist, blood tests, imaging studies
May have preexistent symmetric SNHL due to presbycusis or preexisting noise-induced hearing loss, providing new SSNHL meets other criteria	Self report, history, audiometry
≤14 days since onset of SSNHL	Self report
≤10 days of oral steroid treatment since onset of SSNHL	Self report
Must be able to read or write English or Spanish and repeat words in English or Spanish	Local PI assessment
No history of tuberculosis or treatment for positive skin test (PPD)	Self report; skin test and/or chest x-ray if needed; to be determined by local PI
No insulin-dependent diabetes mellitus	PI assessment, glucose test
No history of rheumatologic or autoimmune diseases	Self report, PI assessment
No history of atherosclerotic vascular disease, coronary	Self report, PI assessment, EKG

artery disease, transient ischemic attacks or cardiac arrhythmia	
No underlying serious psychiatric disease or history of psychiatric reaction to steroids	Self report, PI assessment
No prior treatment with chemotherapeutic or immunosuppressive drugs	Self report
No pancreatitis	Self report
No active peptic ulcer disease or history of GI bleeding	Self report
No known HIV, hepatitis B or C infection	Self report, blood tests
No chronic renal insufficiency	Self report, PI assessment, blood tests and urinalysis
No alcohol abuse	Self report
No active herpes zoster infection (shingles)	Self report, PI assessment
No advanced/severe osteoporosis or nonsurgical (mild) aseptic hip necrosis	Self report, PI assessment
No previous or recurrent unilateral SSNHL	History
No previous hearing fluctuation in either ear	History
No Meniere's syndrome in either ear	History, PI assessment
No chronic granulomatous or suppurative otitis media or cholesteatoma in either ear	History, PI assessment
No otosclerosis in either ear	History, PI assessment, audiogram
No previous ear surgery (except PE tubes in childhood)	History
No congenital hearing loss, even if symmetric or conductive	History, PI assessment, audiogram
No history of blunt or penetrating ear trauma, barotrauma, or acoustic trauma immediately preceding SSNHL	History
No luetic deafness	History, PI assessment, blood tests
No genetic deafness with strong family history	History
No craniofacial anomalies or known temporal bone malformations	History, PI assessment, imaging studies

1.4.5.4 Inability to complete the study

The clinical centers will exclude any potential participant who reports plans to move from the clinical area during the study period. If there appear to be any other obstacles that preclude full participation in the study, the potential participant should not be enrolled.

1.4.6 Sample Size Projections

1.4.6.1 Primary outcome measure

The primary outcome measure for this study is the change in four frequency PTA (based on 500, 1000, 2000, and 4000 Hz frequencies) from baseline to two months after randomization.

1.4.6.2 Hypothesized treatment effect

Our estimate of the expected treatment effect is based upon data from a pilot study of IT methylprednisolone treatment at the Coordinating Center (see Preliminary Studies, Sections 2.1 and 2.2). For a group of 14 participants given IT steroids, the mean change in PTA was 29.1 dB (s.d. 25.6). Among a group of 139 participants treated with oral steroids, the mean change in PTA was 28.0 dB (s.d. 24). For purposes of sample size calculation, we assume a common standard deviation of 25.

1.4.6.3 Sample size calculation

If the change in PTA for the IT steroid group is no more than 10 dB below the change in PTA for the oral steroid group, IT treatment will be considered not inferior to oral treatment. Setting alpha equal to 0.05 as the boundary criterion for significance and power at 90% and selecting a one-sided test for non-inferiority, the required number of randomized participants is 108 per group. Assuming a 10% withdrawal rate, the number of randomized participants needed is 120 per group, or a total of 240. Accounting for three interim looks and a final look at the data, the sample size requirement is 127 per group or 254 total (see Section 1.4.11).

1.4.7 Recruitment Goals

Sample size calculations indicate a need to randomize 254 participants into the two treatment arms. Based on past experience, we conservatively estimate three years of recruitment will be needed.

Recruitment will be centrally coordinated and closely monitored by the Steering Committee. Geographic diversity of the participating Clinical Sites will help assure ethnic and racial diversity in the study population. Initially, each Clinical Site will develop its own recruitment plans, making use of speaking engagements, mailings, internet, press, and broadcast media. These will be reviewed by the SSNHL Steering Committee. An initial central training session for the study will include sessions on general recruitment and retention strategies. Biweekly conference calls among the Clinical Coordinators will help to share information on effective recruitment methods.

1.4.8 Informed Consent

Informed consent will be obtained from each participant at the time of enrollment into the SSNHL study. Extensive efforts will be made to inform potential participants fully of all aspects of the study, including potential risks and benefits and follow-up procedures. In addition, a brochure that describes the study in detail will be given to each participant. After the potential participant has had the opportunity to read and discuss the provided information with study personnel, she/he will be asked to make a decision regarding participation in the study. If the potential participant cannot read the informational documents, a reader/interpreter will be provided. The consent will include permission to use as study data audiometric measures obtained as part of routine clinical care. The participant's full understanding of the overall study is important for ethical reasons and for compliance with the study protocol. A sample consent form appears in section 4.2.1. Privacy and confidentiality policies in compliance with HIPAA requirements and each Clinical Site's local practices will be strictly followed.

1.4.9 Randomization

Participants who meet entry criteria and consent will be randomized into two treatment cohorts. Randomization code lists will be generated prior to start of participant recruitment by the Data Management Center. No one else will have access to these lists. Following determination that the potential participant qualifies for randomization, the study site will contact the Data Management Center to verify the eligibility criteria and obtain the treatment assignment.

The randomization codes will employ a permuted block randomization scheme with each block size a randomly determined multiple of two. A maximum block size will also be selected. Randomizations will be stratified by participating site. Because at least one study [2] has indicated that participants with hearing PTA ≥90 dB may not respond as well to treatment as those with less severe hearing loss, we will also stratify the randomization on the baseline PTA (50 to <90 vs. ≥90 dB).

1.4.10 Study Plan

This section briefly describes the content and flow of the proposed study.

1.4.10.1 Screening and enrollment

The inclusion and exclusion criteria summarized in Sections 1.3.4.1-1.3.4.4 will be supported by data collected in a screening visit that must address the following items:

1) Contact information
2) Informed consent
3) Medical history
4) Demographics
5) Medications
6) Physical examination
7) Otolaryngological examination
8) Laboratory tests
    - Retrocochlear w/u
    - Hct, WBC
    - Banked serum
    - Serum glucose
    - Urinalysis
    - Pregnancy test if indicated
    - FTA-ABS if indicated
    - Other testing if determined necessary by the PI of the site
9) Audiometric evaluation

Once eligibility criteria have been confirmed and informed consent has been obtained, the SSNHL participant will be assigned a study identification number and provided with either a prescription for oral prednisone taper or an initial IT methylprednisolone dose, depending upon randomized treatment assignment. SSNHL staff will review the study protocol with the participants. Participants in the IT injection arm of the study will be scheduled to return twice weekly for the next two weeks in order to receive the remaining three injections and to receive an audiogram at the end of the second week. These visits will be spaced 3-4 days apart. Participants in the oral

treatment arm will be scheduled for an in-person evaluation at one and two weeks post randomization with a follow-up phone call between each of these visits. All participants will be scheduled for an audiogram two months post randomization, a close-out visit, and audiogram six months after randomization.

1.4.10.2 Follow-up: eight weeks after randomization

The main purpose of this visit is to assess the impact of primary therapy on the participant's SSNHL. Participants who have received oral treatment will be instructed to bring their medication bottle for pill count to ensure compliance, a brief medical history will be taken, including a symptom checklist, and an Adverse Event (AE) form will be completed. All participants will have a pain assessment. Any intercurrent events of interest will be noted. Blood pressure and pulse will be measured. Serum glucose, urinalysis, Hct and WBC will be performed.

At this visit the participants will have an audiogram performed. Comparison of this audiogram to the enrollment audiogram will determine the treatment effect. Hearing will be tested again at six months after enrollment as late follow-up to assess the stability of the hearing after completion of treatment.

1.4.11 Early Stopping of the Study

An independent Data and Safety Monitoring Board (DSMB) will be convened by NIDCD to periodically review the study results. The DSMB will decide what information it will need to monitor the study, whether they want to have the two treatment groups identified and whether a stopping rule should be employed.

We propose that interim efficacy analyses for the randomized clinical trial be performed using an alpha spending function approach to control the overall Type I error probability to be 0.05 [46]. This approach was selected because it allows flexibility in the timing and number of interim analyses and these need not be pre-specified. We will use approximate O'Brien-Fleming boundaries [47] so that early interim analyses will be conservative. It is anticipated that the DSMB may request up to three annual interim analyses in addition to the planned end-of-study analysis. If these occur at times when 25%, 50%, and 75% of the study information has been accumulated, the nominal significance levels for these tests will be alpha equals 0.0001 (first interim analysis), alpha equals 0.0055 (second interim analysis), alpha equals 0.0219 (third interim analysis), and alpha equals 0.0479 (final look). The monitoring boundaries allow early stopping for rejection of the null or the alternative hypothesis. East 3.1 was used to estimate the sample size based on these parameters. The target sample size, after adjustment for the expected 10% withdrawal rate, is 127 per group or 254 total.

1.4.12 Adverse Events; Serious Adverse Events

When interventions are initiated, the participant will be briefed on the possible side effects of the interventions and the medical significance of these possible side effects. Medication-related AEs that may be encountered during the course of the trial include (but may not be limited to):

1.4.12.1 Oral prednisone

1) Gastritis or GI bleeding
2) CNS events (severe insomnia, nervousness, anxiety, psychosis, mood disorders, and depression)

3) Weight gain
4) Diabetes; can become insulin-dependent
5) Hypertension
6) Cataracts
7) Osteopenia
8) Vascular necrosis of bone
9) Compression fracture
10) Myopathy
11) Serious infections

1.4.12.2 IT methylprednisolone

1) Chronic tympanic membrane perforation
2) Conductive hearing loss
3) Otalgia
4) Otitis media
5) Any of AEs on oral prednisone list (1.4.12.1)

These AEs will be evaluated and managed by the Clinical Site investigators as deemed appropriate. Management may include counseling, use of other medications (e.g., antacids, antihypertensives, sedatives, or antihyperglycemics), consultative evaluation by other nonstudy physicians, or termination of study medication. Adverse events will be reported to the Data Management Center on the appropriate forms developed for this purpose.

The following are considered **Serious Adverse Events (SAEs)**:

1) Septicemia
2) Meningitis
3) Suicidal ideation
4) Uncontrolled high blood pressure
5) Uncontrolled diabetes
6) Vascular necrosis or compression fracture
7) Any other health-related event that, in the attending physician's opinion, necessitates interruption of assigned medication

All SAEs (during the initial study participation will require a full medical work-up and notification of the Study Chair and the Chair of the DSMB. Any minor health-related events (AEs, e.g., minor infections, drug side effects, etc.) will require focused assessment by the Clinical Site physician.

The following information will be recorded for any health-related AE that occurs during the study: nature, onset, and any remedial action taken. All health-related AEs must be reported to the Data Management Center. Serious adverse events will be reported to the Study Chair, the DSMB, and the Data Management Center within 48 hours. Adverse events will be reported on forms during regularly scheduled mailings.

The DSMB will routinely review information concerning all AEs, particularly those of a serious nature.

1.5 DATA TO BE COLLECTED

1.5.1 Primary Outcome Measure: Audiometry

The aims of this study require the sensitive capture, quantification, and description of treatment effects in SNHL. The site of lesion of SSNHL is the cochlea and the optimum tests are those which concentrate on that site and are comparable across participants rather than those which strive to include the effects of linguistic context (sentences), retrocochlear processing (HINT), and personal coping (HHI). For this reason, pure tone thresholds were chosen to provide both sensitivity and cochlear tonotopic information in a standard clinical setting. Monosyllable word recognition was chosen to provide a well understood metric of information passing through the cochlea under optimum conditions. These tests are specifically designed to concentrate on cochlear function and, as much as possible, remove other variables such as cognitive ability, distractibility, sensitivity to handicap, complex timing, and unmasking abilities (noise and reverberation). These tests will be the outcome measures of this investigation in order to provide both sensitivity and focus to an investigation of changes in participants' cochleae under treatment conditions.

Models of Variability

When using standardized methods (ANSI S3.21-1978) the variability of any given auditory threshold has been established as plus or minus 5 dB or one step size [48,49]. This study will use the common practice of combining thresholds in the central audiometric frequencies (0.5-4KHz) into a PTA. Pure tone average is a commonly accepted way of reporting both audiogram data in groups and also treatment effects [50]. Mathematically combining the four thresholds (using discrete 5-dB steps) in a linear average produces an expected confidence interval ($p<0.01$) of 3.75 dB. Therefore, this level of variability is expected *a priori*. In pilot studies and in the literature, much larger variability is presented by the actual disease and treatment effects.

In terms of recovery from disease, the allowable range of values for both thresholds and PTA is restricted by the starting severity. For example, the maximum possible recovery of an ear with a starting PTA of 30 dB HL is only about half that of an ear with a PTA of 60 dB HL. Pilot studies indicate a treatment effect for steroids of about 20 dB PTA with a standard deviation of about the same size. This means that for starting severities less than 40 dB PTA it is possible that effects would begin to exhibit a floor effect as described above. In this study, the clinical entity happens to produce a severe to profound loss, and so all starting severities will be ≥50 dB PTA. It is likely therefore, that no bias will be introduced by restriction of possible recovery values.

The best model of the variability of monosyllabic word recognition is that of Thornton and Raffin [51]. These authors treat the test as a set of binary outcomes (correct and incorrect) and therefore distributed as a binomial variable. Such a variable's confidence interval will vary based on the location of the data point near the center (50%) versus the extremes (0% or 100%). For example, the recorded 50-item lists for use in this study have a 95% confidence interval as large as 18% near the 50% correct point, and as low as 4% at either extreme. Judgments of significance will be made by referral to the table published by these authors. The method of taking the data will also allow comparison of other methods, such as fixed percent criteria.

1.5.2 Secondary Outcome Measures

A number of important secondary outcome measures will be collected in order to interpret more fully the relative benefits of study treatments.

1.5.2.1 Treatment discomfort assessment

Pain and discomfort may attend the use of IT steroids. This is partially mitigated by a mixture of 2% lidocaine with the methylprednisolone. In order to assess the severity of this treatment side effect, we will administer a Treatment Discomfort Assessment utilizing the Wong-Baker Faces Pain Rating Scale, which features a series of facial expressions in a ten-point visual analog scale and serves as a basic method of communication about pain (section 10.3.13) [52].

1.5.2.2 Serum banking for immunologic studies

At randomization/enrollment a single red-top tube of blood will be taken and banked for possible future immunologic studies. These samples will be drawn locally at the time of other safety monitoring laboratory tests. They will initially be stored locally and then shipped in batches to the UCSD site (J.P. Harris, PI) for permanent storage and possible future testing.

1.5.2.3 Laboratory-based safety measures

Because of the known side effects of the drugs used in this study, a laboratory panel will be used for serial monitoring of potential toxicity from the therapy. An HCT and WBC will be used to follow the possible development of myelosuppression. Serum glucose and urinalysis will be done to look for hyperglycemia or glycosuria, respectively, which could be indicators of steroid-induced diabetes. Each of these tests will be performed locally.

1.5.2.4 Physical exam measures

Blood pressure, pulse, and body weight will be obtained at each visit for all participants but will only be sent to the Data Management Center at visit #1.

1.5.2.5 Symptom checklist and interval history

At each scheduled follow-up examination, a short medical history will be obtained to identify important medical events that have occurred during the time since the last clinic visit. To assess adherence and record concomitant therapy, the participants will also be instructed to bring all study medications and a current medications list.

1.6 DATA ANALYSIS

1.6.1 Primary Analysis of Primary Outcome Measure

The primary analysis will be based on intent-to-treat principles. A two-sample t-test will be done to compare mean PTA changes in the two groups. We intend to include all randomized participants in the analysis grouped according to their originally assigned treatment. We will attempt to follow all participants who withdraw from treatment early to obtain an evaluation two and six months after randomization. We estimate the percentage of participants who will not have a two-month evaluation to be less than 10%.

1.6.2 Secondary Analyses of the Primary Outcome Measure

We will conduct several additional analyses of the primary outcome measure. (1) We will compare mean changes among those participants who completed the full treatment protocol. (2) We will conduct a multiple linear regression analysis to evaluate the magnitude of the treatment effects after adjustment for participant characteristics such as age, gender, duration of SSNHL prior to treatment, and baseline degree of hearing loss. (3) We will evaluate the responses and characteristics of those participants who do not complete treatment to assess the missing response pattern. Following this, we will conduct a longitudinal analysis using mixed-model techniques to characterize the response profiles over time, making appropriate adjustments for nonresponse if the missing response pattern indicated the presence of informative censoring. (4) We will compare mean changes in PTA for the following subgroups: males, females, whites, African Americans, Hispanics, baseline PTA <90 dB, baseline PTA ≥90 dB, with and without associated vestibular symptoms, age (above vs. below median), duration of SSNHL before treatment (above vs. below median), and duration of pre-enrollment steroid treatment (above vs. below median). Because the study is not powered to detect significant treatment effects in subgroups, we recognize the limitations of drawing conclusions if no treatment effect is observed in a subgroup.

1.6.3 Secondary Outcome Measures

Comparisons between treatment groups will be done for the following:

1) Other efficacy measures
   - Word recognition score
   - Difference in PTA between affected and unaffected ear (change from baseline to eight weeks after randomization)
2) Treatment compliance
   - Percentage of participants withdrawing from treatment early
   - Percentage of the prescribed treatment taken (0-25%, 26-50%, 51-75%, and >75%).
3) Safety
   - Percentage of participants withdrawing due to AEs
   - Percentage of participants experiencing an SAE
   - Chi-square tests will be used to compare withdrawal between groups while a two-sample t-test will be used to compare average number of AEs between groups.

1.7 STUDY ORGANIZATION

The organizational structure for the SSNHL study includes the following key components: the Study Chair, the Steering Committee, the Executive Committee, Clinical Sites, Data Management Center, and the DSMB. The specific responsibilities of each are detailed below.

1.7.1 The Study Chair

Steven D. Rauch, M.D., is the PI and Study Chair. His office is located at the Massachusetts Eye and Ear Infirmary, Department of Otolaryngology. Dr. Rauch has primary responsibility for all direct interactions between NIH-NIDCD and the Study, and for direct interactions with the FDA and any other regulatory bodies on behalf of the Study. He chairs

meetings of the Steering Committee and monthly conference calls. He is responsible for providing annual progress reports to NIDCD, semiannual progress reports to the DSMB, and creation of the overall budget for the Study. He makes final decisions regarding any issues of medical inclusion or exclusion that arise at all participating Clinical Sites. He oversees all quality assurance site visits. Dr. Rauch has final responsibility for the overall study compliance, quality assurance, and data integrity.

1.7.2 Steering Committee

The Steering Committee will be the main governing body of the study. Membership of the Steering Committee will include the Study Chair, the PIs of the Clinical Sites, the PI and Study Biostatistician of the Data Management Center, the study's Senior Audiologist, and the NIDCD Project Scientist. All major scientific decisions will be determined by vote of the Steering Committee. Except for the organizational period, the Steering Committee will meet approximately semiannually and will communicate by monthly conference calls.

Subcommittees of the Steering Committee will be established as needed by the Steering Committee. The NIDCD (or its designee) will have a representative on such committees.

Specific functions of the Steering Committee include:

1) Determining the scientific aims of the study
2) Establishing participant eligibility requirements
3) Developing the study design
4) Developing the protocol and participating in the development of study forms and the Manual of Procedures
5) Overseeing implementation of the protocol
6) Establishing subcommittees and task forces, as needed
7) Serving as the scientific forum for the study for reviewing and reporting data
8) Making budgetary decisions
9) Approving all ancillary study proposals
10) Monitoring overall study quality control

The Steering Committee will coordinate the development of protocol for data collection and will provide a continuous review of quality control. It will also monitor the publishing of results, determining whether a methods/baseline manuscript will be prepared, assigning priorities to the publishing of study results, assigning investigators to writing groups, determining the content and form for the presentation of final study results, settling issues regarding authorship, and reviewing and approving manuscripts before they are submitted. The Steering Committee will also set protocol for assigning the ownership and final disposition of data.

1.7.3 Executive Committee

The Executive Committee will monitor day-to-day operations related to the conduct of the study, and, as appropriate, will make decisions on behalf of the Steering Committee. Such decisions, however, will be subject to the concurrence of the Steering Committee membership. The Executive Committee will consist of the Study Chair, one member of the Steering Committee to serve as Vice Chair in the absence of the Study Chair, the PI of the Data Management Center, the study's Senior Audiologist, and the NIDCD Project Scientist.

1.7.4 Clinical Sites

Each Clinical Site will be actively involved in the recruitment, evaluation, and treatment of participants. Each Clinical Site will have a PI (physician), a Clinical Coordinator, and a Lead Audiologist. These personnel will provide the expertise necessary for the successful completion of the protocol.

1.7.5 Data Management Center

The Data Management Center will have primary responsibility for data transmission and management. Its staff will receive, edit, store, and analyze data generated by the Clinical Sites. It will also provide key assistance in designing the data system and be responsible for developing and monitoring data quality control.

Additional responsibilities of the Data Management Center include:

1) Assisting (the Steering Committee) with preparation of the protocol, study forms and the Manual of Procedures
2) Developing the experimental statistical design of the study
3) Working with the investigators in the development and pretesting of forms and procedures, and assuming responsibility for the reproduction and distribution of forms used in the study
4) Training Clinical Coordinators and Lead Audiologists in data procedures, and monitoring data reporting performance
5) Managing quality control aspects associated with the reporting and management of data
6) Summarizing Clinical Site performance, at approximately six-month intervals, for the Steering Committee
7) Providing detailed reports regarding participant recruitment, data collection activities, and interim results to the DSMB
8) Preparing, in collaboration with the PIs, various manuscripts of the study results

1.7.6 NIDCD Office

The NIDCD is the primary funding source for the study. The NIDCD Project Scientist will be a voting member of the Steering Committee, and other members of NIDCD may be invited to attend meetings. The NIDCD Program Office has ultimate oversight of the study.

1.7.7 Data and Safety Monitoring Board

A DSMB will be appointed by the NIDCD and act in an advisory capacity to the NIDCD. The DSMB will consist of a chairperson and additional voting members who are appointed by the NIDCD. *Ad hoc* committee members may be appointed by the NIDCD if deemed necessary. The DSMB meetings will be attended by the NIDCD Project Scientist, the Study Chair, and the PI of the Data Management Center. Meetings of the DSMB will be called by NIDCD at least two times per year.

Specific responsibilities of the DSMB include:

1) Conducting in-depth reviews of the progress of the study at six-month intervals (which will include evaluating participant recruitment and adherence to the protocol)
2) Recommending approval for subsequent changes to the protocol suggested by the SSNHL Steering Committee

3) Reviewing outcome data and making recommendations to the NIDCD regarding continuation, modification, or early termination of the study, should it become necessary to protect the safety and welfare of the participants
4) Assisting the NIDCD in resolving problems referred by the PIs, including SAEs reported according to Section 1.4.12

1.8 STUDY TIMETABLE

The study will have a duration of five years, consisting of three time periods: a six-month planning period, a three and one-half year recruitment and follow-up period, and a one year close-out and analysis period. The Steering Committee will meet monthly by teleconference and in person as needed. Subcommittees of the Steering Committee will meet as needed throughout the study. It is expected that the DSMB will meet semiannually throughout the study.

1.9 STUDY PERSONNEL

The current personnel in each of the positions listed above can be found in appendix A.

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CHAPTER 2
RECRUITMENT AND PRE-SCREENING OVERVIEW

2.1 RECRUITMENT OF STUDY COHORT

Timely and successful recruitment for the SSNHL study will require implementation of a variety of recruitment strategies at each center. Each of the Clinical Sites collaborating in this study has experience with recruitment procedures. An extended recruitment period is planned for all Clinical Sites, beginning by six months into funding Year -01, and continuing through the end of Year -04. All participants will be reassessed at intervals from their time of entry into the study until six months after enrollment. Thus, a total of six months of follow-up data will be obtained on all study participants. The final six months of the study will be devoted to the completion of data analyses and manuscript preparation. A total of 254 men and women will be recruited.

In most clinical trials the single largest challenge is recruitment. The number of eligible participants is frequently overestimated in the planning phase, and the work involved in screening and recruiting participants proves a surprising and difficult task. In addition, the work-up and processing of participants who will eventually prove to be ineligible at the time of randomization is frustrating and time consuming. As such, all efforts should be made prior to the initiation of screening to enhance the identification and appropriate processing of potential participants before the first study visit. These efforts include the development of networks to refer potential participants and a complete understanding of the eligibility requirements.

Each Clinical Site, on average, should plan to enroll 10-12 participants per year to the randomized oral vs. intratympanic steroid study. Our experience suggests that many potential participants must be screened to identify each participant eligible and willing to enroll in the study. Aggressive pre-screening campaigns will be necessary to meet recruitment goals.

Although SSNHL is not a rare condition, it is often misdiagnosed by primary care physicians or treated by community otolaryngologists. Therefore, the identification of individuals who meet eligibility requirements and are referred to the participating study's Clinical Sites will be difficult and will be a primary challenge of the study. Potential participants will be identified within the practice of the participating investigators. Initially, each Clinical Site will develop its own recruitment plans that will be reviewed by the Steering Committee. A Recruitment Subcommittee of the Steering Committee will be created to develop and oversee recruitment efforts of the Clinical Sites. A variety of strategies will be utilized in recruiting participants into the study. It is unlikely that the number of participants needed will be available exclusively from the practice of the Clinical Site investigators. As such, one of the responsibilities of the Clinical Site PIs and CRCs is to broaden the net of potential participants that may be available for the study.

2.1.1 Referral Through Physicians and Clinic

Potential participants will be identified by the Clinical Sites' participating investigators, surgeons, and colleagues in departments of otolaryngology. A special effort will be made to obtain support from local medical societies and clinical subspecialists in each Clinical Site area. We will emphasize the importance of the trial to help the medical community evaluate the role of prednisone and methylprednisolone in reversing or preventing hearing loss among patients diagnosed as having SSNHL.

The first and most obvious source of additional participants is the practice of physicians in the same group as the PI. Given the current clinical environment, the associates of the study's PI sometimes forget or are unaware of randomized clinical trials, and as such, awareness within the practice or department should be reinforced regularly. This reinforcement needs to be both prospective and retrospective. Prospective efforts include reports of study progress at group meetings to heighten awareness and having study materials and reminders prominently displayed. It is also likely that some potential participants will fail to be screened. The CRC should periodically perform chart reviews to ensure that all potential participants are referred. If potential participants are missed, the CRC should encourage the study PI to discuss particular participants with his/her associates and stress the importance of the study to the group. The CRC should be aware of the referral rates of members of the practice, and especially make the PI aware of physicians that chronically fail to refer potential participants.

With the current clinical environment, recruiting participants from beyond the practice is a particular challenge. However, community physicians can successfully be approached to refer potential participants if the need to enroll and monitor participants is separated from their care as patients. Specifically, the study is not requesting that potential participants be referred to the study PI, but rather that they are allowed to participate in a clinical research program. The primary care of the patient can remain under the direction of the community physician; however, the participant must abide by the treatment protocol. The participant must attend evaluations in the study clinic, but may also be seen by the community physician. More importantly, the potential participant is being asked to participate in the study for a finite period of time (active treatment for two weeks with two additional follow-up visits), and the community physician can be assured that all care of the participant will be returned to the community physician beyond that point. Finally, advantages to the community physician should be stressed. These include providing the most current care to their patients and the value of being associated with the leading edge of treatment for a complex disease. These are difficult and time-consuming relationships to develop and foster; however, the opportunity to expand the recruitment net may well be an important and fruitful effort.

It is likely that clinic staff will become aware of potential participants in the daily course of operations. All patients suspected of SSNHL should be pursued and evaluated. In most instances, the physician will have already explained the study to the potential participant. Upon being found eligible through pre-screening, the potential participant will be contacted by the CRC to invite him/her to participate in the study. The potential participant will be scheduled for a screening and enrollment visit where he/she will sign the consent form and be screened to ensure compliance with all eligibility criteria. If the potential participant is eligible and willing to participate, he/she will be randomized into the study. At this visit, the participant will complete the necessary study questionnaires, undergo audiometric evaluations, and, if not yet done, have testing to rule out retrocochlear disease. Baseline laboratory tests will include HCT, WBC, serum glucose, and, if indicated, a pregnancy test. At the discretion of the Clinical Site PI and based upon intake medical history, other diagnostic laboratory tests may include:

PPD	Other immune study
Hepatitis screen	LFT
Syphilis screen	BUN

ANA	Creatinine
RF	Chest X-ray
ANCA	EKG
LE prep	Other cardiac study
Complement	Other
ESR	
HIV	

2.1.2 Self Referral

In some instances an individual may independently learn of the study and want to participate. These individuals may self-refer. Eligible men and women will be scheduled for the baseline visit at which time they will sign a release for obtaining medical records as well as an informed consent form and complete the baseline laboratory and audiology tests and study questionnaires. The participant's physician will be notified as to their decision to enroll in the study.

2.2 INITIAL CONTACT

The initial contact with a potential participant will occur after Clinical Site staff identifies the individual(s) from one of the above described recruiting strategies. The CRC will contact the potential participant by telephone, letter, or at the clinic site. This contact will be followed by a pre-screening and, if initially eligible, an in-person meeting, where the PI or CRC will explain the study to the potential participant, establish eligibility, and obtain informed consent.

2.3 PRE-SCREENING AND ELIGIBILITY

Interested men and women meeting the eligibility criteria should be scheduled for a clinic visit as soon as is convenient. The first recorded contact will be documented using the following: the *SSNHL Screening Log*, the *SSNHL Informed Consent,* the *SSNHL Audiology Data Form*, the *SSNHL Baseline Participant Questionnaire*, and the *SSNHL Baseline Physician Questionnaire*. These forms consist of questions concerning the participant's address and phone number and cover the following eligibility criteria (see Chapters 1 and 6 of the SSNHL MOP for more detailed inclusion/exclusion criteria).

Inclusion Criteria

1) Male and female ≥18 years of age in good health
2) Unilateral SNHL developing within 72 hours
3) Pure tone average (PTA) ≥50dB based upon four frequencies (500, 1000, 2000, and 4000 Hz) in the affected ear with the affected ear ≥30dB worse than contralateral ear in at least one of the four PTA frequencies
4) To the best of the participant's knowledge, hearing prior to onset of the SSNHL was symmetric
5) Hearing loss must be determined to be idiopathic following an evaluation by an otolaryngologist, appropriate blood tests, and imaging studies.
6) Participants may be enrolled if they have preexistent symmetric SNHL due to presbycusis or preexisting noise-induced hearing loss, provided that a new unilateral hearing loss meeting criteria 2 and 3 (above) is present.
7) Participant enrollment must be accomplished within 14 days of SSNHL onset.

8) Participants may be enrolled if they have already begun oral steroid treatment for their SSNHL, as long as that treatment has been for a total duration of ≤10 days, regardless of dose.
9) Participants must be able to read or write English or Spanish. They must be able to repeat words in English or Spanish so that word identification tests can be conducted.

Exclusion Criteria

Any of the following will exclude the potential participant.

Exclusion Criteria for Systemic Disease

The following conditions or situations would contraindicate entry into this study because there would be significant risk of ascertainment (misclassification) bias regarding the correct diagnosis of idiopathic SSNHL or because of significant risk from their disease if such participants were given immunosuppressive drugs. Whether or not the potential participant meets criteria will be determined by the PI at each Clinical Site.

1) >21 days prior oral steroid treatment for any reason within the preceding 30 days or ≥10 days prior oral steroid treatment of SSNHL within the preceding 14 days
2) History of tuberculosis or of prophylactic tuberculosis therapy for positive skin test (PPD)
3) Insulin-dependent diabetes
4) History of rheumatic disease, including rheumatoid arthritis, scleroderma, lupus erythematosus, polymyalgia rheumatica, polyarteritis nodosa, temporal/giant cell arteritis, Sjögren's syndrome, or ulcerative colitis
5) History of unstable angina, coronary artery stenting or bypass grafting within 3 months of enrollment, transient ischemic attacks or stroke within 4 weeks of enrollment, or cardiac arrhythmia
6) Serious psychiatric disease or history of psychiatric reaction to corticosteroids
7) Prior treatment with chemotherapy agents, immunosuppressive drugs (azothioprine, cyclophosphamide, leukoran, or other alkylating agents), or cyclosporine, FK506, etanercept, infliximab, or interferon
8) Pancreatitis
9) Active peptic ulcer disease or history of gastrointestinal bleeding
10) History of known HIV, hepatitis C, or hepatitis B infection
11) Chronic renal insufficiency requiring dialysis
12) Alcohol abuse
13) Active shingles (herpes zoster infection)
14) Advanced/severe osteoporosis or nonsurgical (mild) aseptic necrosis of the hip.
15) General anesthetic for any reason within two weeks of enrollment
16) History of head and/or neck radiation therapy

Exclusion Criteria for Otologic Disease

The following conditions or situations would contraindicate entry into this study because of the significant possibility that they could cause sudden SNHL, resulting in ascertainment bias regarding the correct diagnosis of idiopathic SSNHL as defined herein.

1) History of previous or recurrent unilateral SSNHL
2) History of fluctuating hearing in either ear
3) History of Meniere's syndrome in either ear
4) History of chronic granulomatous or suppurative otitis media or cholesteatoma in either ear

5) History of otosclerosis in either ear
6) History of prior ear surgery of any kind (except ventilating tubes in childhood)
7) Asymmetric SNHL prior to onset of SSNHL
8) Any congenital hearing loss, even if symmetric or conductive
9) History of blunt or penetrating ear trauma, barotrauma, or acoustic trauma immediately preceding SSNHL
10) History of luetic deafness according to criteria outlined by Darmstadt and Harris [1]
11) History of genetic SNHL with strong family history
12) Craniofacial anomalies or known temporal bone malformations as revealed by CT scan

2.3.1 Participant Identification Number and Screening Log

A log of every participant encountered should be kept. Each participant who signs informed consent and participates in the baseline visit should be assigned a Participant ID number that will be used as a unique study identifier. This three digit ID number is assigned sequentially for each potential participant seen by the Clinical Site. The combination of the three digit Clinical Site number and three digit Participant ID number provide a unique identifier for each person screened for the study.

In the event that the potential participant is ineligible or unwilling to participate in the study, the appropriate section of the *Eligibility Checklist* form should be filled out (see Chapter 10) so that the study can keep close track of reasons that potential participants are ineligible for the study.

2.3.2 Screening Log

This log is used to record potential participants who present with unilateral SSNHL, but would not qualify for the study based on information available in the medical record etc. Individuals included in this log were not consented, not randomized, and completed no other study forms. These individuals could be considered "pre-screen failures". Participants who were consented but are excluded in Form 1are not included in this log.

This log will be maintained by the CRC at each site:

1) HOSP	Enter the three-digit clinical site code.
2) Screen#	Enter the three-digit screening number, assigned sequentially beginning with "001".
3) Date	Enter the data the screening took place.
4) M/F	Enter "1" for male "2" for female.
5) Birth Year	Enter the year of the individual's birth. Note: age 90 years or older is considered and "identifier". If age is 90 or greater, enter "99" for the birth year.
6) Screening Method	Specify how the patient was screened (phone, walk-in etc.).
7) Code	Supply the two-digit code for the reason the individual did not qualify for further screening. A maximum of three codes may be entered. In cases where there are more than three, enter what would be considered the three most

	important. See the CODES directory for the Screening Failure Code List.
8) Reason for Failure	Specify why the individual did not qualify for further screening.
9) Referral Source	Specify the source of referral, if applicable.

The screening log should be submitted to the Data Management Center at the first of the month for the previous month's screenings. Please note that this log contains information on individuals who are not consented. No identifying information may be included on this log. The CRC may maintain a separate log linking the screening numbers to individual's names. Such a list must be kept secure at each clinical site only.

2.4 REFERENCE

1. Darmstadt GL, Harris JP. Luetic hearing loss: clinical presentation, diagnosis, and treatment. Am J Otolaryngol 1989;10(6):410-21.

2.5 LOGS

The 1) Screening Log, 2) Telephone Log, and 3) Telephone Conversation Record are located in a folder marked "Logs" in Adobe Acrobat (.PDF) format LOG-[log-name].PDF.

CHAPTER 3

COLLECTING PARTICIPANT INFORMATION

3.1 GENERAL GUIDELINES FOR INTERVIEWING

3.1.1 The Role of the Interviewer

The SSNHL CRC will most often be involved in interviewing participants. The interviewer plays a critical role in the collection of information for the SSNHL study. The interviewer's ability to develop and maintain a positive rapport with the participant will influence initial recruitment, the quality of the data obtained, and the willingness of the participant to remain in the study for its duration. The interviewer's first contact with a participant will set the tone for the entire study. It is important that the interviewer maintain a professional and friendly manner at every contact with the participant. Specific aspects of the interviewer's role are described below.

3.1.1.1 Neutrality and impartiality

In the ideal situation, the interviewer's presence should not influence the participant's perception or response to a question, and different interviewers should obtain the same response from the same participant. Recognizing the limitations inherent in this ideal, there are methods that can enhance the neutrality of the interviewer. First, the use of a structured interview is essential. Second, the interviewers should provide neither verbal nor nonverbal responses that can influence the participant's responses. For example, an interviewer should not show surprise, pleasure, or disapproval to any answer. Even apparently innocuous behaviors like nodding, smiling or sighing will influence the participant's responses to questions. The interviewer's role is to obtain honest, uninfluenced responses to the questions. The interviewer should be a neutral medium through which questions and answers are transmitted.

Similarly, it is important for the interviewer to convey a sense of impartiality. He or she should be gracious and adaptable to all participants regardless of whether their dress, appearance, style of speech, or personal preferences are consistent with the interviewer's values and preferences. The participant should have confidence in the interviewer and feel that his or her responses are important.

3.1.1.2 Appearance and demeanor

Clean, neat, professional dressing and style are important. The interviewer's dress and demeanor should convey that he or she is an appropriate representative of the medical community, that the research is important, and that the participant is a respected member of the study.

The demeanor of the interviewer should be casual, yet professional. This is a difficult balance to maintain and requires a thorough familiarity with the questionnaires and procedures prior to interviewing the first participant. Although it is essential that the structured interview be followed verbatim, the interviewer should not sound like an automaton. The interviewer should know the questions so well that it never sounds as if he or she is reading them formally. The interviewer should use a natural, conversational style. At the same time the interviewer needs to stay on track and politely, but firmly, lead the participant through the interview.

Finally, the interviewer should be pleasant and friendly. A major objective is to put the respondent at ease. If the participant isn't relaxed, the interviewer can't make the participant talk. Similarly, the burden of ignorance has to be lifted from the respondent's shoulders -- that is, he or she must not be made to feel ashamed of his/her lack of information. The interviewer's attitude, therefore, must be sympathetic and understanding. Emphasize that there are no correct answers. Rather, the participant must realize that what he or she thinks really is what counts. An opinion can never be wrong.

3.1.2 The Interview

3.1.2.1 Do's and don'ts

In their text on Survey Research, Backstrom and Hursh-Cesar provide a list of the do's and don'ts in conducting an interview. These are paraphrased below to fit the context of the SSNHL study.

Never do any of the following:

1) Never get involved in long explanations of the study. Use the standard responses given you.
2) Never deviate from the study introduction provided for the study. Do not invent your own explanations.
3) Never suggest an answer and never agree or disagree with an answer.
4) Never change the sequence of questions. Read them exactly in the order written.
5) Never try to ask questions from memory.
6) Never rush the participant. Let the participant understand the question fully. Don't show impatience.
7) Never patronize participants who do not speak standard English.
8) Never react to answers. Do not smile, grimace, gasp, laugh, frown, query, agree, disagree - or anything else.
9) Never do anything that suggests to the participant that an answer is right or wrong.
10) Never dominate the interview. Your job is to get information, not give it.
11) Never record a "don't know" answer too quickly. People say, "I don't know," when stalling for time to arrange their thoughts. The phrase merely may be an introduction to a meaningful comment, so give the participant a little time to think.
12) Never interview someone you know; turn the interview session over to someone else at the Clinical Site.

Always do each of the following:

1) Always study all questions until you know what they mean and are familiar enough with them so you can really ask the questions instead of reading them blindly.
2) Always interview yourself for practice, answering each question thoughtfully. Then interview someone else, again for practice.
3) Always reread your instructions between interviews.
4) Always check with the Data Management Center whenever you encounter difficulties with questionnaire wording or procedures.

5) Always be polite.
6) Always act naturally.
7) Always be firm about interruptions and privacy.
8) Always complete the interview at one sitting.
9) Always use the response categories provided for each question.
10) Always record and explain every answer in the correct place.
11) Always repeat and explain questions if the participant does not understand.
12) Always keep talking as you write.
13) Always focus the participant's attention on the questions.
14) Always take the blame for faulty communication. If the participant stumbles, say that perhaps you didn't read the question clearly or read it too rapidly. Don't ever let a participant feel the questions are too difficult for him or her.
15) Always accept a refusal graciously and naturally. Don't react.

3.1.2.2 Probing for responses

Even in closed-response categories, probing is sometimes required. Probing is a critical technique to master, as it is an easy place to fall prey to directing responses or altering the meaning of a question. Thus, probes must be as uniform as possible within and across centers.

If the participant provides an inappropriate response to a question (e.g. uses the wrong response category), repeat the question and the response categories. For example, if the interviewer asks a question that requires a participant to provide his or her degree of agreement and, instead, the participant says, "That's true," the interviewer responds, "Would you say you strongly agree or agree?"

If a participant provides an ambiguous response to a question, then the interviewer must obtain an elaboration to the response without directing the response. Specific probing techniques are listed below:

1) Echo the participant's exact answer while raising your inflection at the end to form a question.
2) Repeat part of the question.
3) Wait for further clarification while still looking at the participant.
4) Request that the participant rephrase his or her response.
5) Nod, smile, or say yes to encourage further elaboration by the participant.
6) Ask a question to get a more specific comment.
7) Whenever there is some confusion between the interviewer and the participant, the best thing for the interviewer is to repeat the question, verbatim.
8) Neutral questions or comments are frequently used to obtain clearer and fuller responses. Examples of these are: "Anything else?" "Any other reason?" "Any others?" "How do you mean?" "Could you tell me more about your thinking on that?" "Would you tell me what you have in mind?" "What do you mean?" "Why do you feel that way?" "Which would be closer to the way you feel?"
9) Indicate slight bewilderment and your failure to understand. For example, state, "I'm not quite sure I know what you mean by that -- could you tell me a little more?"

The interviewer must remember that the balance between probing and directing responses is a difficult one to maintain. The interviewer must be sure that he or she is merely eliciting clarification and not pushing the participant to respond in a particular manner. Also, the interviewer must judge when to stop probing and go on to the next question. The participant should not be made to feel that he/she is ignorant or that his/her responses are inadequate.

3.1.3 Privacy and Confidentiality

It is critical that each interview be conducted in a quiet, private area within the Clinical Site. Each clinic should have a designated area that is comfortable for the participant and free from intrusions.

Interviews will generally be conducted by the CRC, who will complete data forms during the interview. Participant's spouse/partner, friends, or relatives may be present if the participant wishes them to be. If someone is with the participant and is reluctant to leave despite their request, explain the necessity of privacy for study purposes and be prepared to suggest places where this individual can wait comfortably.

Participants are assured of confidentiality and it is critical that confidentiality be maintained throughout the study.

An interviewer must often ask questions that one would not think of asking even a close friend. Most people, however, are willing to answer such questions when they are asked in an interview. They are willing to give information because they trust that it will be used only for serious purposes. Your protection of all information about participants gained during the conduct of research is therefore essential. This means to protect not only the information you get in direct answer to the questions you ask in an interview, but also the information you gather through incidental observations of the participant.

It is important that care be taken in maintaining confidentiality of completed questionnaires while in your possession. Always make sure that questionnaires are not left where non-research staff can view them. You must safeguard the completed questionnaires by not leaving them unattended, such as in your car where they might be stolen or in a school room, clinic room or office where anyone could walk in and read them.

It is your duty to keep the promise of confidentiality. Never divulge names or tell facts about or reveal the opinions of anyone you interview.

Information collected or seen during an interview can be shared only with the research team, whose members are under the same ethical or moral obligation as you are to the people interviewed. As you may know, persons who participate in research studies have rights to privacy that are protected by Federal law. Maintaining confidentiality of data is not just a philosophical issue for an interviewer. It means that an interviewer must be aware of the importance of protecting the confidences of the study participants on a day-to-day basis. For example, a comment to a friend outside of the research team about a particular participant or their response is a breach of confidentiality and is unprofessional conduct as an interviewer.

3.1.4 Preparation for Interview

The interviewer should:

1) Review the MOP and training materials.

2) Go through the structured interview carefully.
3) Organize all the necessary materials, including pencils, extra paper, a clipboard, etc.
4) Be certain the interview room is neat and organized.
5) Review the information available on the participant and information needed for the interview (e.g. time of appointment, name of participant, etc.).
6) Be certain his/her appearance is appropriate for the interview.

3.1.5 Conducting the Interview

The interviewer should record all responses by clearly marking the appropriate category and not overlapping between categories. Questions should be read and explained, if necessary. Interviewers should go slowly and speak naturally. If participants do not respond, the questions should be repeated. The interviewer should be able to determine a comfortable pace for the participant after the first two or three questions.

3.1.6 Editing the Interview

It is critical that interview forms be carefully reviewed immediately following an interview. This point should be kept in mind when participants are scheduled so that the interviewer has allowed adequate time, following the interview, to edit the preceding interview and prepare for the next interview. Regardless of who enters the data, the interviewer should edit as if she or he will not have any future opportunity to clarify a response. That is, once an interview form is edited well, anyone trained in data entry should be able to enter the interview data with no problems.

Editing includes:

1. Rereading every question and being certain that the response category is unambiguous. If necessary, the correct response should be printed to the side of the question.
2. Printing responses to all open-ended questions and eliminating abbreviations, initials, etc. that were used during the interview to save time and maintain a comfortable pace with the participant.
3. Recording any unusual issues that arose with specific questions.
4. Making certain that every question is accounted for. If a participant refused to answer a question or did not understand it, this should be recorded. Also, if the interviewer accidentally skipped a page or question, this should be recorded. (See Chapter 17 for the proper codes to use for missing information.)

3.2 GUIDELINES FOR ADMINISTERING QUESTIONNAIRES

Many of the general rules for governing interviewers' conduct are also applicable for the self-administered questionnaire that is a part of SSNHL. Only a single form, *SSNHL Self Report Form*, is self administered. All other questionnaires will be completed by CRC in an interview setting. Specific considerations for self-administered questionnaires follow.

3.2.1 Literacy Difficulty

While the self-administered questionnaires are designed for ease of administration, for a variety of reasons you can anticipate that a number of respondents will have difficulty completing the questionnaires by themselves. Approximately 6% of the American population (with a range from 2-13% across individual states) is formally considered functionally illiterate, having completed fewer than four years of schooling. This rate is probably a gross underestimate of the number of individuals who are likely to have difficulty completing a self-administered questionnaire because of problems in

concentration, reading fluency, or comprehension. In addition, a number of respondents will have vision problems or difficulty in writing responses.

While we cannot accurately estimate the number of participants in SSNHL who will have literacy or vision difficulties, some participants are likely to have problems in this regard. It is important to provide these participants with the opportunity to have the questionnaires administered by the interviewer. When handing the questionnaire to the respondent, the interviewer should say to the respondent, "We have found that some people prefer to have the questions read to them. Would you like me to read these questions to you?" If the respondent says, "No," the interviewer should indicate availability to answer any particular question which may arise during completion of the questionnaire.

3.2.2 Confidentiality and Comfort

As with other interviews, it is important to indicate to the participant that his/her responses to this questionnaire are confidential.

Assist the respondent in finding a comfortable, quiet place to complete the questionnaire. If this place is not in the immediate clinic area, it is important that you take responsibility in making sure that the participant is returned to familiar surroundings once the questionnaire is completed. If the participant is completing the questionnaire while waiting for a procedure or the doctor, it is your responsibility to monitor the time for the participant or assist in making arrangements for a short delay. The participant should not have to be worrying about a missed appointment while he or she is completing the questionnaire.

Be sure that the room is tidy and ready and that any needed supplies, such as pens and forms, are available.

We ask that the participant complete the questionnaire without the help of a spouse or friend, and you should discourage others from staying with the participant while he/she is completing the questionnaire. Although this may not always be possible, you should reinforce the value of the participant's own responses.

Emphasize again that you are available to answer any questions that may arise.

3.2.3 Respondent Questions

The interviewer should be familiar with all questions and their meaning. In response to requests for clarification, reread the question exactly as it appears, stressing by your voice intonation references to time, place, and question intent -- for facts or feelings. Do not ad-lib an explanation of the question. It is critically important to stay with the literal expression of the questions since this is the best way to ensure that data collected at the many clinical sites are comparable.

3.2.4 Respondent Complaints

Always take blame for problems with the questionnaire and attribute them to the people in the office. For instance if the respondent complains of particular wording or redundancy or length of the questionnaire, say, you don't know why it was done as it was, but it is important for the respondent to answer as best they can.

3.2.5 Completeness

Stress the importance of completing the questionnaire without interruption. However, it is reasonable for the participant to take a short break, if he/she so desires.

3.3 SELF-ADMINISTRATION

3.3.1 Self administration

If it has been determined that the participant is able to complete the questionnaires on his or her own, introduce the questionnaires to the study participant by telling them that questionnaires contain questions about their health history and symptoms.

It is sometimes useful to tell participants that there are no right or wrong answers on the questionnaires. It is often helpful to tell this to the participant if any uncertainty or hesitation is observed. It is important to put participants at ease.

In addition, the clinic staff should read over the directions to the questionnaires with the participant and then leave him or her to complete the forms in privacy. The staff person should remain in the area, however, in case the participant has a question or needs some other form of assistance.

3.3.2 Checking the Returned Questionnaire

When the questionnaire is returned, the SSNHL CRC should spend a few minutes (usually only 2-5) checking it over while the participant is still there. Check first for omissions and missing information.

Review the questionnaire for completeness and legibility immediately following participant completion. Prior to the participant's leaving, ask to take just another few minutes to be sure that nothing is missing and review the questionnaire for unanswered questions, ambiguous answers, or illegibility. If there are unanswered questions, ask the participant if this was intentional. If so, simply continue going through the form (the informed consent statement clearly reminds the participant that he/she may decline to answer any particular question). If the participant indicates that he/she did not intend to leave out a question, ask him/her to complete the unanswered question. If there are ambiguous responses, such as double markings or unclear erasures, ask for clarification. Be sure you can read any open-ended responses.

CHAPTER 4

INFORMED CONSENT GUIDELINES

4.1 INTRODUCTION

The success of every clinical trial depends on the cooperative participation of its participants. For the SSNHL study to succeed, the potential participants will be required to consent to enrollment, complete a two-week course of treatment plus a five-day taper for participants in the oral treatment arm, appear for all follow-up visits as indicated, and report any side effects that may develop. To aid in meeting these objectives, we must try to obtain truly informed voluntary consent. If the consent process is simply a mechanical ritual, the trial could be jeopardized by a large number of early dropouts, poor adherence to interventions, and confusion about study protocol. Informed consent may be obtained by the Clinical Site PI, other participating clinic physicians, or the site CRC if so authorized by the site PI. The consent form must have a date-stamped IRB approval (yearly IRB approval with date stamp).

4.2 BASIC ELEMENTS OF INFORMED CONSENT

The Department of Health and Human Services (DHHS) guidelines set forth eight essential elements of informed consent:

1) Participants must be advised that the study involves research. An explanation must be given regarding the purposes of the research, the expected duration of the subject's participation and a description of the procedures to be followed, including identification of any experimental procedures.

It is essential that the potential participant understand that his or her treatment assignment will be determined by chance. The potential participant will have an equal chance of being assigned to either the oral or IT treatment group.

It is especially important that potential participants be given a clear understanding of the purpose of the two treatment groups. This calls for an explanation of the scientific approach to the study and the need to control as many variables as possible. By emphasizing the importance of the route of treatment administration and the uncertainty about whether the two study treatments are equivalent, we explicitly call attention to the fact that this is primarily a study, rather than a therapeutic program that has been specifically designed for an individual patient.

We should carefully explain that this is a randomized trial in which neither the potential participant nor the doctor can dictate which treatment group the potential participant is assigned to. To allay anxiety, it is important to note that those individuals involved in safety monitoring will be able to identify the participant's treatment assignment immediately in an emergency situation. A panel of national experts (Data and Safety Monitoring Board [DSMB]) will be continually informed as to what is happening to each treatment group. If an active treatment group proves to be significantly harmed, the study may be stopped, at least for those who might be harmed. Experts who have access to all the data from the trial are in the best position to judge the relative effectiveness or harm of active treatment to the participants or special subgroups of the participants.

Potential participants should be told that they are expected to attend the formal screening/eligibility visit. During the first visit (1) they will have a physical exam, their blood pressure and weight will be measured and (2) they will be asked to complete a series of

laboratory and audiology tests, and (3) they will be asked to complete a variety of questionnaires about their health, medical history, and the medications they are taking. If they are still eligible for the SSNHL study and agree to participate, they will then receive two weeks of steroid treatment plus a five-day drug taper for participants in the oral treatment arm. At the next visit, two weeks after beginning primary therapy, (1) their blood pressure and heart rate will be measured, (2) they will have blood and urine samples taken for laboratory tests, (3) an audiometric evaluation will be obtained, and (4) they will complete additional questions on health symptoms and adverse events. They will be seen again for check-up and audiometry at two subsequent follow-up visits.

All participants will be requested to attend all screening visits, safety monitoring and follow-up visits, and take their study medications. Potential participants should have a clear idea of the time demands of the study, the side effects of study drugs, and the importance of safety monitoring tests. To avoid misunderstanding, it should be made clear that their participation in the study is expected to last for six months.

2) Anticipated benefits of the trial must be explained to participants.

Many participants appreciate the opportunity to be involved in relevant research and to contribute to medical knowledge. In the SSNHL trial, the knowledge we gain may or may not be specifically applicable to participants in the study. Results from the study will provide knowledge about future treatment of SSNHL and may be an added benefit of participation.

Research in SSNHL has shown that primary oral prednisone therapy can benefit some patients. However, it does not achieve full recovery in the majority. Animal research and anecdotal human trials have suggested that IT methylprednisolone may achieve equal or greater benefit. The potential side effects and risks of oral and IT steroids differ. The goal of this SSNHL project is to study whether primary treatment with IT steroid is equivalent to oral steroid treatment.

There are several important reasons to study the effects of these drugs on hearing loss. First, it is probable that both treatments will improve hearing in many study participants. Second, we will learn important information about the way steroids act in the ear. If IT therapy has better outcome, it will indicate that this route of drug administration is more effective, possibly because it achieves higher drug concentration in the inner ear. Furthermore, if either treatment is significantly more effective than the other, this will be the basis for adoption of the better treatment by clinicians. If, on the other hand, oral and IT treatments have equivalent efficacy, then the potential side-effects and adverse events associated with each become critical factors in physician and patient decision-making about treating future cases of SSNHL. Either way, the outcome is likely to have a strong impact on future standards of care for SSNHL.

All participants in the trial will be monitored closely. Diagnostic or safety monitoring tests that are routine standard of care will be billed to third party payers as appropriate. Charges not covered by insurers will be borne by the study and are provided at no cost to the participant.

Of course, there is no way of knowing in advance whether a particular participant will personally benefit from active treatment during the course of the trial. This will depend on whether the medications are effective. We should be careful not to suggest that participants will benefit from active treatment simply by entering the trial. If we were convinced that the interventions were effective, we would not be conducting the trial. The study may show that participants in the IT group do as well or better than participants on oral treatment.

3) Attendant discomforts and risks must be described.

Participation in the SSNHL study may involve some added risks and discomfort but every attempt will be made to closely monitor all participants. To reduce the risks, we have purposely excluded those for whom the study is contraindicated.

However, in spite of our precautions, participants may experience risks and discomfort which include the following:

a) There is a very small chance of pain, a bruise, and a possibility of infection at the site of a venipuncture (where the blood is drawn). Fainting may result from the venipuncture procedure.

b) Prednisone is a powerful anti-inflammatory agent and may cause side effects such as mood changes, weight gain, appetite increase, bruising and thinning of the skin, osteoporosis (thinning of the bones), and increased risk of atherosclerotic vascular disease. Other side effects that might occur include cataracts, diabetes mellitus, high blood pressure, muscle weakness, glaucoma (increased eye pressure causing pain or loss of vision), and stress fractures resulting from osteoporosis. Prednisone treatment may suppress the immune system and cause an increased susceptibility to infections. The participant should be told that study visits and laboratory monitoring will be used to monitor any potential problems.

c) Methylprednisolone is also a potent anti-inflammatory agent. Since it is being administered in small volume directly into the middle ear via injection through the ear drum, it may cause local side effects such as pain, transient dizziness, middle ear infection, or persistent ear drum perforation. Since some portion of the middle ear dose may flow down the eustachian tube and be swallowed, participants receiving IT methyl-prednisolone are also exposed to all the potential risks of the oral prednisone treatment group.

4) Appropriate alternative procedures that might be advantageous for the participant must be disclosed.

This mandate is often overlooked in written consent forms. It means that the potential participant should be told what options exist if he or she elects not to participate in the trial. The potential participant should be told that the alternate treatment available would include conventional use of oral prednisone therapy, with no randomization to IT treatment.

5) The extent to which confidentiality of records identifying the participant will be maintained must be described.

Confidentiality of all participant information is assured in all participating centers. No unauthorized personnel should have access to participant records or results of interviews or tests. Additionally, all record storage rooms should be appropriately secured, and should contain necessary locked files or other storage equipment.

It may be useful to explain that in studies of this nature, numerical and alphabetic codes are assigned by which central study files may be linked to individual participants. Participants are not identified by name in any reports or publications.

6) Potential participants must be advised of the availability or non-availability of medical treatment or compensation for physical injuries incurred as a result of participation in the study, and, if available, what they consist of or where further information may be obtained.

It may be useful to distinguish between providing study treatment and follow-up free of charge and financial compensation for injuries incurred. The Federal Government is prohibited by law from committing funds that have not yet been appropriated by Congress, and no funds have been allocated for compensating injured participants in trials such as SSNHL. The only recourse for such participants is to seek compensation through the courts or through negotiation with the Clinical Site involved.

Reimbursing the cost of medical treatment for a research-induced injury is a separate issue. Every effort will be made by the Study Chair's Office and the Clinical Sites to reimburse injured participants for their medical expenses if the participants are required to pay such costs out of their own pockets. Any such problems will be dealt with on a case-by-case basis.

Policies regarding compensation and reimbursement vary from institution to institution, so we cannot recommend a standard approach for all participating sites. Staff members should stress the fact that the chance of serious injury in SSNHL is small but the Government requires that compensation be discussed with potential participants if there is any risk at all. Legal terms and concepts should be translated into lay person's language, and the ideas should be made relevant to the SSNHL study, not simply to research in general. Comments regarding compensation should be as brief as possible.

7) Persons responsible for the study must offer an explanation of whom to contact for answers to pertinent questions about the research and the participant's rights, and whom to contact in the event of the development of side effects, a medical emergency, or a research-related injury to the participant.

We suggest that one or more persons associated with the trial be available to answer relevant questions while potential participants are contemplating participation.

Potential participants should be handed the names of these people on a card when they are first approached. If no names are provided, they may ask questions of persons not knowledge-able about the study and be given unclear answers or misinformation.

Once they are enrolled in the study, we recommend that participants receive written information regarding whom to contact at any time about possible side effects during therapy or rights as a participant in the study.

8. Participants must be told that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which he or she is otherwise entitled.

We obviously would like each of our participants to remain in the study until the end of the trial, if possible, but they have the right to withdraw at any time. We must communicate this option to potential participants without luring them into the trial on a probationary "look and see" basis. Hesitant potential participants should be evaluated very carefully to screen out those who are likely to withdraw early.

The right to withdraw from a trial is compromised if such behavior invokes penalties. This is the reason for the phrase, "without penalty or loss of benefits," and the idea should be explained to potential participants. If they drop out of the trial, the act of dropping out will not jeopardize their regular care.

The eight requirements of informed consent in the DHHS guidelines above refer primarily to categories of information that enable potential participants to make rational decisions regarding participation in clinical trials. Except for the stipulation that participant inquiries should be answered, these basic elements do not refer to the process of obtaining informed consent.

4.3 THE PROCESS OF OBTAINING CONSENT

Various studies indicate that the circumstances under which consent is obtained in clinical trials can have a profound influence on the potential participant's interpretation of information communicated during the consent discussion and on the freedom of potential participants to make their own decisions.

Given the data at hand, we are recommending the following guidelines to ensure that the consent we obtain will be as informed and voluntary as possible:

1) Potential participants should be fully informed about the study and have adequate time to evaluate the pros and cons of participation.

Sudden sensorineural hearing loss is a straightforward study of an urgent problem. Delay in initiation of treatment can compromise outcome. The benefit of prompt treatment must be balanced against the need for potential participants to make a fully informed choice to participate. Because of this, it is recommended that the CRC review the informed consent with the potential participant and answer any questions. The Informed Consent Form may then be sent home with the potential participant so that he or she may more carefully review it if necessary.

2) Potential participants should be encouraged to discuss the study with anyone they wish, particularly family and friends who might be affected (for example, persons who might be needed to provide transportation).

Close associates of the potential participant may raise questions and considerations that the potential participant has overlooked, and questions that concern the family are better answered sooner than later. Furthermore, there is evidence to suggest that family support for studies of this kind increases the probability of participant cooperation during the course of the research.

3) To be eligible for participation in the SSNHL study, potential participants must have the capacity to give their own informed consent.

If a potential participant is incapable of understanding what is expected of him or her as a participant in the study, it is not permissible to obtain informed consent from a guardian. The study requires daily responsibilities that cannot be easily assumed by other persons. The potential participant is also free to discuss participation with his or her personal physician.

4) The setting in which consent is obtained should be as private as possible so potential participants can freely ask questions without embarrassment.

If extraneous parties can hear the conversation, potential participants may be reluctant to ask appropriate questions.

5) To avoid pressuring the potential participant, only one person associated with the study should be present when the potential participant reviews the consent forms.

If a second witness is required, he or she should be as unobtrusive and non-committal as the situation permits.

6) The potential participant should be given a copy of the informed consent forms after they are signed and witnessed.

The witness cannot be a person involved with the study. Even though participants are free to withdraw from the study at anytime, the consent form details our obligations to the participant and the participant's obligations to the study while he or she is enrolled.

7) Potential participants should be encouraged to keep the consent forms.

The consent forms contain useful information about the study which participants may want to review from time to time. After the potential participant has signed the consent form forward the consent form to the PI for his signature.

4.3.1 Sample Consent Forms

MASSACHUSETTS EYE & EAR INFIRMARY

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Protocol Title: Sudden Hearing Loss Multicenter Treatment Trial

Steven D. Rauch, MD, and associates are conducting a research study to compare the effectiveness of two different treatments for patients with sudden deafness. Sudden sensorineural hearing loss (SSNHL) is an ear emergency in which the hearing in one ear drops in less than 72 hours. Prompt treatment with oral prednisone can often improve the hearing, but few patients make a full recovery. There are some indications that delivering medicine directly into the ear rather than orally is equally effective and could have potential advantages such as avoiding oral steroid side effects. The two drugs being studied, oral prednisone and injectable methylprednisolone, are both well known anti-inflammatory steroids. Methylprednisolone is approved by the FDA for other uses but is investigational for this study. Injecting steroids into the ear has been gaining popularity in clinical practice but has not been studied scientifically to see if it is truly safe and effective. Thus, for this study the injection therapy must be considered experimental. We plan to enroll approximately 250 study participants nation-wide at eight participating medical centers. On the basis of your hearing tests and examinations, and the history of your current ear problem, you have been invited to take part in this study.

If you agree to be in this study, the following will happen to you:

Procedures: All participants will be randomly assigned to receive either 19 days of oral prednisone or two weeks of methylprednisolone injections (twice weekly injections for a total of four doses). By "random" we mean that neither you nor any of the clinic staff (including your doctor) can select your treatment assignment. Using a procedure similar to flipping a coin, a computer program determines what treatment group you will enter. In both cases, the duration of treatment is similar and the drugs have similar actions. However, the route of administration will be different. It is important to remember that you do not have an option of choosing your treatment assignment in the trial.

Your participation in the study will last six months. You will be seen one week, two weeks, two months, and six months after enrollment. These follow-up visits are standard treatment for anyone with SSNHL, regardless of study enrollment or not. At each data collection visit we will test your hearing. At enrollment and at each follow-up visit we will take blood and urine samples for safety monitoring lab tests. We will use the blood to test for possible side effects to the medication. With your permission, we will store some of the blood for possible additional research immunology tests in the future. We will also ask you to complete questionnaires to update our records on your medical history, to note any symptoms, and to keep track of any other medications you are taking. Most clinic visits will last from one to two hours.

Risks/Discomforts: Participation in this study may involve some added risks or discomforts. These include:

1) Pain and bruising or the possibility of infection may occur at the venipuncture (blood sampling) site. Dizziness and fainting may result from the venipuncture procedure.

2) Treatment with steroid drugs (prednisone and methylprednisolone) may cause side effects which are more properly termed complications from the use of this drug. Side effects that

may be expected to occur in this study include mood changes, weight gain, appetite increase, bruising and thinning of the skin, osteoporosis (thinning of the bones), and increased risk of atherosclerotic vascular disease. Possible side effects that might occur include cataracts, diabetes mellitus, high blood pressure, muscle weakness, glaucoma (increased eye pressure causing pain or visual loss), and stress fractures resulting from osteoporosis. Prednisone treatment can cause an increased susceptibility to serious infections by lowering immunity. Methods will be used to try to minimize the incidence and severity of these complications and they include using the drug at a single daily dose, counseling participants to continue their exercise program, and making sure that all participants are followed by their general internist so that there is appropriate prevention and treatment of osteoporosis. Laboratory monitoring and study visits will be used to monitor potential complications. You will be given an information sheet with instructions about what side effects to watch for and when to contact your physician or other study personnel.

3) Since the methylprednisolone is being injected directly through the ear drum, it may cause local side effects such as pain, transient dizziness, middle ear infection, or persistent ear drum perforation.

Participants in this study will be encouraged to avoid aspirin and medicines like Motrin because they may cause stomach upset (gastric side effects) that may worsen problems caused by steroids.

Since this is an experimental treatment there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

If you are pregnant or a nursing mother, you will be included in this study only after the study physician has received clearance for your participation from your obstetrician. If you think you might be pregnant, you must notify the doctor so a pregnancy test can be performed. You may have to withdraw from the study.

If you are injured as a direct result of participation in this research, the Massachusetts Eye & Ear Infirmary will provide any medical care you need to treat those injuries. The Infirmary will not provide any other form of compensation to you if you are injured. You may call the Research Administration Department at 617-573-3009 for more information about this, to inquire about your rights as a research subject, or to report research-related problems.

Benefits: There may or may not be any direct benefit to you from this treatment. The investigator may learn more about the treatment of SSNHL with the drugs prednisone and methylprednisolone.

Costs: All standard patient care costs will be billed to your insurance company. Any costs not covered by insurance will be born by the research study. These costs may include audiograms, laboratory tests (blood, urine, MRI scan), and treatment medications.

Confidentiality: Every effort will be made to safeguard the information you provide us. Records from this research study will be kept confidential to the extent provided by law and not given to anyone who is not helping in the study, unless you agree to have the records released. However, the FDA, the Data Management Center at the Hines VA Hospital, and the sponsor of this study (the National Institutes of Health) have the right to review your research records, including your medical chart. Neither your name nor any set of personal identifiers will be

entered into the Data Management Center computers. In order to insure that we can keep in contact with you, we will record some personal information on a participant contact form and this information will be stored in a locked file cabinet under the supervision of the principal investigator.

Alternative treatments are available for you and consist of standard oral prednisone primary SSNHL treatment or no treatment at all. There are no alternative procedures known to benefit SSNHL at this time. In addition, your participation may be terminated by the investigator (Dr. Rauch) without regard to your consent if you need additional medication, violate the study plan, experience a study-related injury, or for administrative reasons.

Dr. Rauch or one of his associates has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Rauch at 617-573-3644, or you may direct questions to the Massachusetts Eye & Ear Infirmary, Research Administration at 617-573-3009. Participation in research is entirely voluntary. You may refuse to participate or you may withdraw at any time without jeopardy to the medical care you will receive at this institution

You have received a copy of this consent document to keep. You agree to participate.

_____ _____

Participant's Signature Witness Date

_____ _____

Investigator's Signature Witness Date

____ I agree to participate in this study but do NOT wish to have a serum sample stored for future immunology research studies of sudden sensorineural hearing loss.

_____ _____

Participant's Signature Witness Date

CHAPTER 5
AUDIOLOGY PROCEDURES

5.1 INTRODUCTION

The purpose of this section of the manual is to support the audiologists in their task of providing data which is complete, valid and comparable. To this end, this section will focus on specifications of equipment, materials and data cross check mechanisms to ensure this goal. First, the *SSNHL Audiometry Worksheet* (section 5.5) (Figure 5-1) will be filled out during each evaluation. This worksheet will not be transmitted to the Data Management Center, but will provide supporting information in order to specify equipment, sound levels and test materials used to develop the data. Second, the audiologist will analyze the result, apply specific coding conventions (see sections 5.6.2-3) and fill out the *SSNHL Audiology Data* form (Chapter 10). This form will contain the primary outcome data for the study. At the initial screening of each prospective participant (visit 1.0 only), the audiologists will also fill out an *SSNHL Audiology Eligibility* form (Chapter 10) to provide analysis of the audiometric screening results in the specific terms of the study inclusion criteria.

The text in this section is designed as a resource for audiologists in the completion and disposition of all audiology forms used in this study. The purpose of the audiometric evaluation is to supply precise and valid auditory thresholds at traditional frequencies to be used for participant inclusion and as outcome measures. In addition, a standardized word recognition procedure will allow reliable evaluation of the effect of disease and treatment on information passing through the affected ears. The following procedures will concentrate on these two straightforward goals, and the wider range of audiologic tests will be presented in a framework which allows the audiologist to use them as needed to assure validity.

5.2 AUDIOLOGY PERSONNEL

The primary source of reliability and validity will be the qualifications of the clinical audiologists performing the tests, and their adherence to standard practices. These practices will be specified in this section. A secondary source of reliability and validity will be the oversight of the local Lead Audiologist appointed for each Clinical Site. Besides on-site evaluation of the data for completeness and adherence to procedure, the Lead Audiologist will compile information assuring standard calibration, installation of reference-calibrated equipment, etc. [1]. The local Lead Audiologist will also act as a stable contact on behalf of their center. Finally, the Senior Study Audiologist (MEEI) will provide a final layer of assurance by developing and updating the procedures in this manual in response to any problems and by maintaining regular contact with each site's Lead Audiologist.

5.2.1 Lead Audiologist

Each Clinical Site will designate a Lead Audiologist who will be the contact for study-related issues with the Senior Study Audiologist. This audiologist will oversee local audiology operations and also communicate with the site PI and CRC. The lead audiologist may train other audiologists at the site for testing.

5.2.2 Qualifications

Each evaluation will be performed by a fully qualified audiologist. The precise definition of qualification can vary from state to state depending on licensure laws, etc. For

the purposes of this study, full qualification is defined as the highest local level of qualification, certification or licensure. Each of these requires a Master's Degree (or higher) and completion of a clinical fellowship or equivalent. Basic requirements for Lead Audiologist will be no different, but only one audiologist per center will be designated for this duty.

5.2.3 Training

Each site's Lead Audiologist will be responsible for local training of any audiologist actually testing. This training will be based on this Manual of Procedures (MOP), and the MOP will remain available to all trained audiologists as a resource. The MOP can be refined and changed (see Chapter 15.2: Changes in the Manual of Procedures) to better accommodate the needs of the local audiologists for precise guidance. All Lead Audiologists will be contacted in advance of the initiation of participant enrollment at the site, and the Senior Study Audiologist will discuss and demonstrate the procedures contained in this manual. These will include personnel, test protocols, data cross checking, procedures for correcting or completing evaluations, and reporting results.

5.2.4 Contacts

A system of regular contact between the Senior Study Audiologist and each Lead Audiologist will be initiated before any participant's enrollment. This will take place primarily by e-mail, with documents faxed as necessary. The Senior Study Audiologist will chair monthly conference calls to monitor and discuss the local status of personnel, training, equipment, and data acquisition. Progress will be discussed and reported formally by the Senior Study Audiologist to the Steering Committee on a quarterly basis. As audiologic issues arise, the local audiologists will be asked to contact the Lead Audiologist, who will act as liaison with the Senior Study Audiologist. Other local issues are expected to be addressed by contact between the Clinical Site PIs, their Lead Audiologists, and the CRCs.

5.3 AUDIOLOGY FILES

Each Clinical Site's Lead Audiologist will, at the commencement of the study, create a filing system for audiology facility records and correspondence. System features will be at the discretion of the Lead Audiologist, incorporating the local filing protocols. However, at minimum this system will contain three recognizable sections: general information, correspondence, and worksheets.

5.3.1 General Information Section

This section will include site-specific information as to the identification of the PI, the Lead Audiologist, Senior Study Audiologist, and others associated with the study, along with extensive contact and coverage information. This section will also include the local location of the MOP, and the data reporting protocol along with copies of calibrations and other equipment records sufficient to document validity. Finally, the General Section will include a comment log, in which dated and initialed entries by any audiologist may make note of any events or concerns.

5.3.2 Correspondence Section

This section will include records of conference calls and other correspondence regarding procedural issues, changes in equipment or personnel, and any adverse events.

5.3.3 Worksheet Section

This section will include all worksheets generated for each audiologic evaluation related to this study. Copies of the audiogram on the local form should be attached to the worksheet.

5.4 AUDIOLOGY TESTING PROTOCOL OVERVIEW

Participants will be referred for each evaluation by the Clinical Site's PI or CRC, who will determine the timing of return visits. When the participant arrives for each test, the audiologist will greet the participant and accompanying persons and briefly and privately discuss progress if the participant wishes. If the participant requires language interpretation, this will be provided in the customary manner in place at each site. Only minimal history taking (i.e. otalgia) is required of the audiologist, and, as much as possible, study questions should be referred to the PI or CRC. Audiologists will not be formally blinded as to the study arm of the participant, but no effort will be made to specify the participant's status to the audiologist, and the previous evaluations will not be reviewed in advance.

The audiologist will seat the participant in a sound-treated room [2]. No more than one person will be allowed to accompany the participant and this person will not be allowed to sit in the booth or to be in the line of sight of the participant. As much as possible, light levels in the participant and the tester sides will be adjusted to provide a good view of the participant and a poorer view of the audiologist (i.e. participant side bright, tester side dark). The participant should be seated perpendicular to the audiologist to minimize cues. The room door will be fully closed. The participant will be asked to respond by hand raise or by button push, whichever is customary at the Clinical Site. The audiologist will use a headphone for monitoring the stimulus (never the speaker) since one ear of these participants is expected to be normal and may possibly appreciate the monitoring sound though the sound booth wall.

The Lead Audiologist at each site will ensure that threshold tests are performed in the standard manner [3]. This includes the Hughson-Westlake bracketing procedure [4, 5]. A 200 ms. ON versus 200 ms. OFF duty cycle for tone presentation is recommended with an opportunity to appreciate 4 tones per trial. Narrow band noises or FM modulated tones will not be substituted for standard pure tones. Thresholds will be transcribed on the Clinical Site's standard audiogram, using standard symbols [6]. At the conclusion of the evaluation, the audiologist may briefly discuss the result with the participant and accompanying persons, again referring most study questions to the PI or CRC where possible. Discussion of helpful strategies and devices as indicated by the case is expected.

5.5 THE AUDIOMETRY WORKSHEET

The *SSNHL Audiometry Worksheet* (Figure 5-1) is designed to be filled out by the audiologist during a standard audiologic evaluation, and to capture specifics as to transducers, test materials, masking used, etc. As it is filled out, the *SSNHL Audiometry Worksheet* will guide the audiologist in terms of completeness and standardization of materials. This worksheet will be filled out at each evaluation in this study. These worksheets will be kept on site in files provided for that purpose by the local Lead Audiologist. There is no flexibility in reporting of the

Site	Participant	Pt. Initials	Visit	Date of Visit
				/ /

SSNHL AUDIOMETRY WORKSHEET

Affected Ear Right 1 Left 2

Bone Conduction

	250	500	750	1000	1500	2000	3000	4000
Unmasked								
Right Masked								
Masking								
Left Masked								
Masking								

Air Conduction

	250	500	750	1000	1500	2000	3000	4000	6000	8000
Right										
Masking										
Transducer										
Left										
Masking										
Transducer										

PTA DATA:

	Right			Left		
500		Air	Masked Bone		Air	Masked Bone
1000		Air	Masked Bone		Air	Masked Bone
2000		Air	Masked Bone		Air	Masked Bone
4000		Air	Masked Bone		Air	Masked Bone

Word Recognition

Right %		CID W-22 Q/Mass	Left %		CID W-22 Q/Mass
Level dBHL		Spanish CD	Level dBHL		Spanish CD
Masking			Masking		
Transducer		List:	Transducer		List:

Valid: YES NO: Describe below **Sound Booth ID**:

Audiologist Comments, Other Test Results and Measurement Issues:

Evaluating Audiologist

Site Lead Audiologist Review and Comments

Site Lead Audiologist

Figure 5-1

threshold and word recognition data, but there are sections included in the worksheet for the flexible reporting of additional tests and measurement issues by the local audiologists.

5.5.1 Header Section

The top line of the form is devoted to identification of the site, the participant, the study visit number and the date. Each site will be furnished with a three-place number to identify the site. This number will be made available to all local audiologists by the Lead Audiologist and will be listed in the General Information section of the study files. The participant's ID number and participant's initials as used in the study will be made available by the local CRC. he CRC will also specify the visit number, indicating the progress of each participant through the study. The date field will be filled out to reflect the date of the evaluation, even if some items result from a subsequent review.

5.5.2 Affected Ear

The affected ear of the participant will be specified by circling the number (1 or 2) in the appropriate box. It is noted that the affected ear is reported redundantly throughout the study documentation.

5.5.3 The Sound Pathway

The testing audiologist will perform a visual inspection of both ears using an otoscope. If there is sufficient access to the tympanic membrane to allow testing, the audiologist will proceed. If there are concerns as to cerumen or other factors, the audiologist may elect to perform tympanometry. When complete, the outcome of tympanometry will be noted on the form (in the section marked "Audiologist Comments…"), and the local report form for such a test (i.e. printed tympanogram) will be dated and included in the file. It is important to note that all middle ear concerns (including perforations) are strictly at the discretion of the PI or clinic physician. Certain middle ear effects may arise during the study and do not necessarily contraindicate testing. The testing audiologist will refer such concerns to the PI or clinic physician before testing. A brief note on the outcome of this interaction may be written in the "Audiologist Comments" area.

5.5.4 Reporting Auditory Thresholds

The next sections on the worksheet require the entry of auditory thresholds. All such entries will be written clearly as integers in the boxes provided. The exception will be when the limit of the equipment is reached without a response. When this occurs, the audiologist will report this as the capital letter "N" followed by the equipment limit level (i.e. "N120").

5.5.5 Vibrotactile Thresholds

Vibrotactile thresholds will never be reported. On discussing the nature of the percept with the participant and determining that they are vibrotactile, the audiologist will mark the response as "out at limits" (see section 5.5.4). When filling out subsequent forms (*SSNHL Audiology Data* form and *SSNHL Audiology Eligibility* form), vibrotactile thresholds will never be allowed to enter into interpretation as audiologic threshold data or indications of any air-bone gaps.

5.5.6 Bone Conduction Section

The audiology threshold section begins with unmasked bone conduction. This test is mandatory in all cases, but actual test order is at the discretion of the local Lead Audiologist. Unmasked bone conduction is the only variable in the masking equation, and so it may be advisable to begin with these data in severe unilateral cases, such as those expected in this study.

5.5.7. Masked bone conduction

The primary purpose of bone conduction is to rule out significant middle ear inefficiency. If any air-bone gaps (larger than 10 dB) are found, masked bone conduction will be required at all mandatory frequencies until the sensory threshold of both ears is resolved. Masked bone conduction is expected to be required in the affected ear with the single exception of recovery of all thresholds to within 10 dB of the unaffected ear. Effective masking will be calculated and the masking will not exceed the calculated value by more than 15 dB [7]. The exception to this will be performance of a masking plateau procedure at the discretion of the audiologist [8]. The audiologist will record the masking level used to determine each masked threshold in the data form in the box below each frequency.

5.5.8 Air Conduction Section

The air conduction section is designed to be used in a similar manner as the bone conduction section, except that entries lacking a masking value will be assumed to be unmasked. Masking will be applied for each threshold where the possibility of crossover exists. The possibility of overmasking will be evaluated by the audiologist and may be addressed, for example, by using insert phones.

5.5.8.1 Transducer

Air conduction thresholds may be evaluated using both standard headphones (TDH-39, 49, 50) or calibrated insert phones (Etymotic ER-3A), as long as specific correction factors are in place [9]. The transducer type (i.e. TDH-49, ER 3-A) should be entered on the *SSNHL Audiometry Worksheet*, reflecting the method by which the final recorded threshold was obtained. It is not anticipated that this should often change for each frequency, but such events are possible when masking dilemmas are encountered, and this is the means of specifying the action taken.

5.5.9 Pure Tone Average Data Section

The PTA reported on the *SSNHL Audiometry Worksheet* is designed to reflect the sensitivity of the participant's cochleae. The object of the PTA Data Section is to allow the audiologist to apply the relevant principles to the decision as to which audiometric thresholds should be used to calculate the PTA. For example, if a participant in the IT arm of the study presents with a 25 dB air-bone gap, the masked bone levels would then be the best reflection of the cochlear sensitivity. These are recorded in the relevant boxes in the PTA Data Section and the method by which they were obtained (air vs. masked bone) will be indicated by circling the appropriate box. Mixed methods are allowable if the audiologist decides that this would give the most accurate PTA. It is important to note that out-at-limits values will remain coded as "Nxxx" in this section. The audiologist will apply

a coding procedure (adding one 5-dB step) later when the data is recorded on the *Audiology Data* form.

5.5.10 Speech Intelligibility Section

Speech intelligibility will be evaluated for each ear using standard word recognition of monosyllables [10]. All tests will use recorded lists (English: CID-W22, Ira Hirsh recording, Q/MASS v 2) [11] from a compact disk supplied by the Senior Study Audiologist [11], including standardized score sheets. The Auditec Spanish bisyllable test will also be provided and may be used at the discretion of the audiologist. Each disk contains a calibration reference 1 KHz tone (track 1) which will be used to set the input sensitivity (V.U. meter) to "0" before each set of tests. A check box is provided on the *SSNHL Audiometry Worksheet* to verify which recording was used. If Spanish is used, the tester must be a fluent speaker of that language. Since the results are analyzed as repeated measures, a participant may be evaluated using English materials if the local audiologist decides that the results reasonably reflect comparative (test to test) performance. In such a case, the participant may be instructed to produce the sounds of the words, even if they do not necessarily recognize the meaning. Any alternate languages, recordings, etc., must be approved by the Senior Study Audiologist. All lists will be recorded (no live voice tests) and 50 items always given.

5.5.10.1 Setting the speech test level

The principal guiding level setting for speech tests is: The level should be set where maximum performance is expected for each ear. In this particular study, word recognition is expected to be performed at high levels, at least on entry (PTA ≥ 50 dB HL), so a limited dynamic range is anticipated. Also, performance has been shown to be quite poor in some sudden hearing loss cases [12], so an empirical search using many levels may introduce more challenges to validity than it would solve. Fortunately, Fletcher's Articulation Index [13, 14] provides a fully developed and

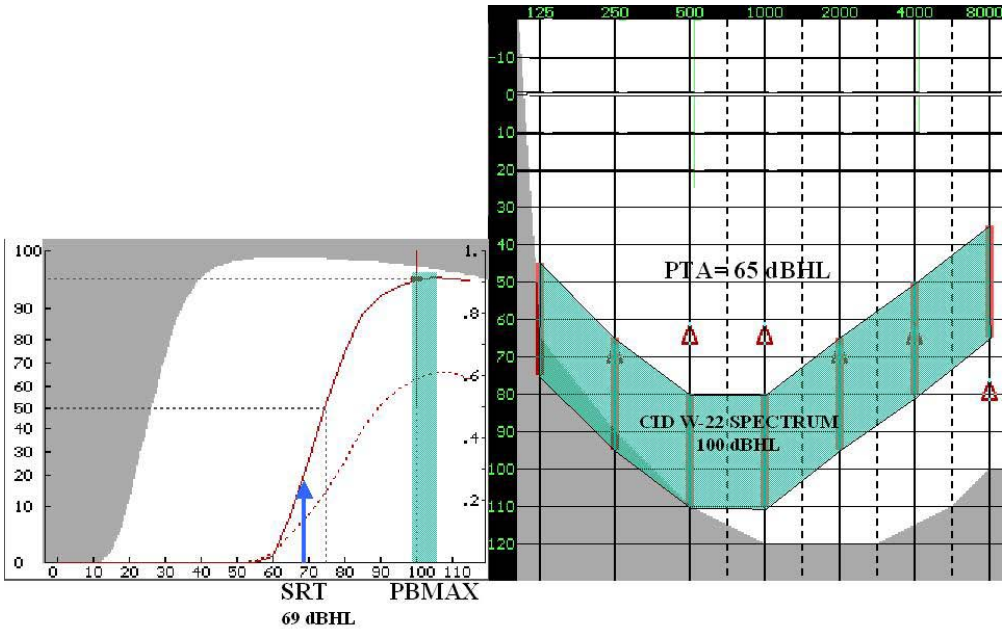

Figure 5-2

standardized (ANSI, 1969) model for performance/level interactions. This formula can be used to draw a cumulative (ogive) optimum performance/intensity (P/I) function for any audiogram (Figure 5-2). The maximum performance would be expected at levels on the asymptote of the curve. This is not to say that the actual performance will be predicted [15], but the curve will reliably co-vary with actual performance such that whatever maximum performance may be, it will be found at the asymptotic level of the predicted P/I function [16]. Using software developed for this purpose [17], Table 5.1 was created for setting speech levels:

PTA2	Monosyllable level
30	-
35	-
40	70
45	75
50	80
55	85
60	90
65	95

Table 5-1

The PTA2 parameter designates Fletcher's 2-frequency average [18]. PTA2 is the average of the two best (lowest) thresholds of the set 500 Hz, 1 KHz and 2 KHz. This value is easy to calculate and delivers better performance predicting speech reception threshold (SRT) and other speech level values than the more inclusive PTAs [19]. The levels were developed Monte Carlo fashion by submitting a representative sample of audiograms to the P/I function generator and relating the PTA2 to the lower levels of the asymptotic portion of the curve. The step size is 5 dB. Smaller gradations are available on some audiometers and may be used at the discretion of the audiologist. No level is required lower than 70 dB HL. The advantage of this minimum level is that normal, mild, and moderate loss cases can all be tested at the same physical level [20]. The level is somewhat high for this reason, but in use in over 100,000 cases at Massachusetts Eye and Ear Infirmary, it has not been shown to produce either discomfort or rollover.

This table is designed to replace rule-based level setting schemes since they are not optimal, especially given the severe losses (PTA $\geq$ 50 dB HL) required for entry to this study. For example, a common rule requires a further test (SRT) to allow levels set at SRT + 40 dB. While this provides reasonable maximum performance for milder cases, with severe losses the dynamic range is reduced below the 40 dB constant. On the other hand, no rule or table can replace good clinical sense when very high levels are required. In abandoning the table values, the audiologist will be asked to decrease levels minimally below the participant's Uncomfortable Level (UCL) rather than set the level at a determined Most Comfortable Level (MCL). The maximum performance is not expected at MCL in these cases and the loudest reasonable level should be used [21]. No levels should exceed 95 dB HL.

5.5.10.2 Participant responses

Participants with poor speech intelligibility are expected to initially report no response (i.e. "I can't get it"). The audiologist is required to explain that guessing is very helpful and that, in order for the test to proceed, the participant must guess a monosyllable each time the carrier phase is heard. Instead of reporting no recognition, a "wild guess" will be substituted. This strategy will optimize responses in cases of low speech intelligibility and is surprisingly effective with participants who are really only uncertain. Dropped plurals are to be scored wrong. If the participant responds with several options, the first one said will be scored. Items will not be repeated. Small variations in regional dialect (i.e. vowel boundaries) are scored at the discretion of the audiologist. Fifty items will be given unless the audiologist is convinced that the participant has no speech-like percept at all. Fifty wrong guesses will be scored as 0% and this represents an optimal test by both the participant and the audiologist. If there is no speech-like percept at all, the test can be scored CNT (could not test). Skipping the word recognition test and entering the notation "DNT" (did not test) is never acceptable. The audiology evaluation will be considered incomplete if the notation DNT appears. Under no circumstances will half-lists or screening lists be performed.

5.5.10.3 Masking for word recognition

Masking will be applied to the contralateral ear during speech tests if there exists a possibility of significant contribution due to crossover [22]. To facilitate this application for this study, the Articulation Index was again used to calculate the maximum score possible by crossover given the difference in PTA2 and the effective masking required to reduce this contribution to zero [23]. This is given in Table 5-2.

Speech Level minus Non-test PTA2	Speech Noise TDH	Speech Noise Inserts
50	15	-
55	20	-
60	25	-
65	30	-
70	35	10
75	40	15
80	45	20
85	50	25
90	55	30
95	60	35
100	65	40

Table 5-2

Table 5-2 includes values based on published interaural attenuation values for both TDH phones (ANSI, 1978) and insert phones (ISO, 1994). Standard speech-shaped noise [24] is assumed in this calculation and will be required as the masker used at the study centers.

5.5.11 Validity Checkbox

If the audiologist determines that the test is valid she/he will check the "Validity" box and need not enter any further information regarding validity. If the audiologist decided to perform other tests (for example SRT, OAE to rule out functional loss) this will be noted along with the outcome in the section marked "Audiologist Comments". As stated in the introduction, the audiometric focus of this study is limited to thresholds and word recognition. In most cases, the principles and procedures outlined above will allow reliable and valid data. One example of an exception requiring different tests would be when functional hearing loss (pseudohypoacusis) is suspected. Hesitant threshold responses or a history of litigation for loss are some of the many warning signs audiologists use to initiate tests to rule out functional loss. In this study, audiologists, supported by their local Lead Audiologist will rule out functional loss on a case-by-case basis. For example, SRTs may be done to evaluate the match with the pure tones [25]. Since participants admitted are expected to have a unilateral severe loss, Stenger's test [26] may be performed. Otoacoustic emissions are not expected in cases of severe loss [27]. Auditory brainstem response (ABR) may be useful for both site of lesion and functional screening. The section marked "Audiologist Comments, Other Test Results and Measurement Issues" will also be used to convey any testing issues such as participant cooperation, noise, equipment issues, etc., which might adversely affect validity.

5.5.12 Audiologist Comment Section

The audiologist performing the test will add any necessary comments in the "Audiologist Comments" section and sign to verify the data and comments.

5.5.13 Lead Audiologist Review and Comment Section

The Lead Audiologist will be responsible for cross check activities but may have another audiologist independently review tests they themselves have performed. Cross check and any actions taken will be briefly noted in the box marked "Center Lead Audiologist Review Comments". Any items requiring more extensive written explanation will be addressed in a separate report attached to the *SSNHL Audiometry Worksheet*. As noted above, the form will then be placed in the local *Audiometry Worksheet* file section. The next step will be that the audiologist will fill out the *SSNHL Audiology Data* form.

5.6 AUDIOLOGY DATA FORM

The study uses repeated audiologic measures designed to capture changes with treatment and with time. Therefore, the *SSNHL Audiology Data* form (Chapter 10) is designed as a uniform data entry form for every test. This form will be filled out for each eligibility screening, and for participants at week 1 (start of week 2), week 2 (start of week 3), 2 months and 6 months. The *SSNHL Audiology Data* form will be filled out during or immediately after each evaluation by the testing audiologist. On completion, the form will be signed and given to the Lead Audiologist for review. The Lead Audiologist will give the form to the CRC for transmission to the Data Management Center.

5.6.1 Header Section

The top line of the form is devoted to identification of the site, the participant, the study visit number and the date. Each site will be furnished with a three-digit number to identify the site. This number will be made available to all local audiologists by the Lead

Audiologist in the general information section of the study files. The participant's ID number and participant's initials as used in the study will be made available by the local CRC. The CRC will also specify the visit #, indicating the progress of each participant through the study. The date field will be filled out to reflect the date of the evaluation, even if some items result from a subsequent review.

5.6.2 Pure Tone Average Data Section

This section is filled out differently than the PTA data section described in section 5.5.9. The principle underlying this form is that the audiologist will apply specific coding protocols so that an integer value will be entered in every box corresponding to a test frequency. Data Management Center personnel will not be required to make the audiology coding decisions. Specifically, if a finding of "No Response at Limits" is found at a frequency during the evaluation, the audiologist will add the next audiometric step (+5 dB) to the value and enter the result. For example, if no response was found at 120 dB HL at 4 KHz on the right, the value "125" will be entered in the box marked "4000" and a "1" will be placed in the corresponding "NR" box to signify that the audiologist had applied the extrapolation rule in this case. Extrapolated data if entered will be used by the audiologist to calculate the value reported in the "PTA" box. In the simpler case, standard thresholds will be entered as found and the "NR" box will be left unmarked. All other boxes will be filled in all cases. A positive value less than 100 will be entered with a leading zero, and negative values will be entered with a leading minus sign.

5.6.3 Word Recognition Section

The principle underlying this section is that the audiologist will apply a specific coding protocol so that an integer value will be entered in each box corresponding to "Right%" and "Left%" data. Here again, Data Center personnel will not be required to make the audiology coding decisions. Specifically, if a finding of "CNT" is made during the evaluation, the audiologist will code the result as "0" and enter "1" in the CNT box. For example, if no speech percept was reported by the participant for Right Word Recognition, "0" will be entered in the box marked "Right%" and the audiologist will place a "1" in the "CNT" box . In the simpler case, standard percent correct results will be entered as found and the "CNT" box will be left unmarked.

5.7 AUDIOLOGY ELIGIBILITY FORM

The purpose of this form is to allow the audiologist to complete the report of the initial screening audiogram in the specific terms of the study inclusion criteria. This form will be filled out by the audiologist once for each participant. This will occur immediately after the first *SSNHL Audiology Data* form is completed for each new prospective participant. The audiologist will record the threshold values and combine these values into PTAs for each ear. The audiologist will compare the results to the study criteria, listed on the form, and make the determination whether the participant is audio logically eligible. On completion, the form will be signed, given to the Lead Audiologist for review and given to the CRC for transmission to the Data Management Center.

5.7.1 Header Section

The top line of the form is devoted to identification of the site, the participant, the study visit # and the date (as in Sections 5.5.1 and 5.6.1 above).

5.7.2 Baseline Threshold Section

This section is filled out similarly to the PTA Data Section described in section 5.6.2. Specifically, if a finding of "No Response at Limits" is found at a frequency during the evaluation, the audiologist will add the next audiometric step (+5 dB) to the value and enter the result. For example, if no response was found at 120 dB HL at 4 KHz on the right, the value "125" will be entered in the box marked "4000". Extrapolated data if entered will be used by the Audiologist to calculate the value reported in the "PTA" box and the "Difference (dB)" box. In the simpler case, standard thresholds will be entered as found. Leading zeroes will be used and leading minus signs are allowed where appropriate. The right or left "Affected Ear" item will be circled to specify the affected ear.

5.7.3 Eligibility Section

The audiologist will circle the boxed numbers (1 or 2) to signify each audiologic eligibility criterion. The audiologist will also circle the boxed numbers corresponding to "Eligible" or "Not Eligible" item to signify overall Audiologic eligibility.

5.8 DATA CROSS CHECKS

This section will describe data cross check activities performed by the testing audiologist and the Lead Audiologist, as well as the mechanism for reporting unforeseen problems or concerns.

5.8.1 Testing Audiologist

The primary data cross checks will be the responsibility of the testing audiologist. Specifically, equipment and training will be maintained which will allow such procedures as masking plateau verification, tympanometry, SRT, Stenger's test, distortion product otoacoustic emissions (DPOAE), and ABR. These tests will be applied at the discretion of the testing audiologist to verify results and to rule out functional or retrocochlear hearing loss. None of these tests will be used as data, but will be noted on the *SSNHL Audiometry Worksheet* and attached to that worksheet.

5.8.2 Lead Audiologist

The testing audiologist will complete the *SSNHL Audiology Data* form, with the exception of the section for Lead Audiologist Review and Comments. The form will then be given to the Lead Audiologist or placed in the file section for data awaiting review. The Lead Audiologist will verify the audiologic aspects of the data. The Lead Audiologist will verify validity and completeness, or will contact the CRC for rescheduling for other testing if necessary. The completed form will be given to the local CRC for transmission to the Data Management Center.

5.8.3 Problems and Concerns

The Senior Study Audiologist will be responsible for resolution of problems in audiology data interpretation. If these arise at the Data Management Center, they will be communicated to the Senior Study Audiologist (i.e. not the local Lead Audiologist directly), who will have discretion as to resolution study-wide or site-specific. If problems arise at an individual site, they will be communicated by the local Lead Audiologist to the Senior Study Audiologist, who will again be responsible for resolution either study-wide or site-specific. The anticipated mechanism for resolution of study-wide issues will be

communication with all local Lead Audiologists and changes or additions to the MOP. The Senior Study Audiologist will be responsible for informing and receiving advice and approval from the Study Chair and the Executive Committee as appropriate.

5.9 REPORTING

The *SSNHL Audiology Data* form will be filled out by the audiologist at each evaluation and given to the local Lead Audiologist for review. The completed form will be given to the local CRC for local record keeping and for transmission to the Data Management Center.

The *SSNHL Audiology Eligibility* form will be filled out for each potential participant screened (Visit 1.0). The completed form will be given to the local CRC for local record keeping and transmission to the Data Management Center.

5.10 REMOTE AUDIOLOGIC EVALUATIONS

The last Visit (# 8.0) and certain others under special circumstances may be performed at audiology facilities not directly attached to the local Clinical Site. Visit #'s 1, 4 and 6 may not be done in this manner. The following section details the procedure for remote audiology evaluation.

5.10.1 Personnel and Responsibilities

The Clinical Site PI and/or the CRC may determine the need to explore a remote evaluation for the purposes of completing data collection. The local Lead Audiologist will be primarily responsible for managing the remote evaluation process. The Lead Audiologist will determine a suitable audiology clinic and assist the CRC in scheduling. The evaluation must be performed by a fully qualified audiologist (See section 5.2.2). The local Lead Audiologist will receive the pure tone audiogram, word recognition and any other results from the remote site, evaluate them and fill out the data form (#3). From then on, transmission via the CRC will proceed in the standard manner. The evaluating (remote site) audiologist will fill out the audiometry worksheet (See Section 5.5) in addition to their normal audiometry reporting. Results may be faxed to the local Clinical Site for convenience.

5.10.2 Materials

When the Senior Study Audiologist is advised by the Clinical Site Lead Audiologist of the arrangement for a remote audiology evaluation, the Senior Study Audiologist will send a packet of materials to the remote site. This will include instructions, the audiometry worksheet form, the Compact Disk of word recognition test materials, score sheets and MOP chapter 5 for background information. Test results will not be returned to the Senior Study Audiologist, but will be received and processed through the local Clinical Site by the Lead Audiologist.

5.11 EQUIPMENT

The following section contains specifications for equipment used in this study.

5.11.1 Sound-treated Enclosure

A single- or double-walled sound-treated enclosure that meets American National Standard Criteria for Maximum Permissible Ambient Noise Levels for Audiometric Test Rooms [2] shall be used to conduct pure tone air and bone conduction thresholds and word recognition testing.

An illuminated otoscope is used to examine a participant's ear canals. If any possible contraindications to audiometric testing (such as excess cerumen, eardrum abnormalities, etc.) are detected, the participant must be referred for medical evaluation before audiometric testing can proceed.

5.11.2 Acoustic Immittance Equipment

An immittance device that meets the American National Standard Specifications for Instruments to Measure Aural Acoustic Impedance and Admittance [28] is used to conduct tympanometry and acoustic reflex threshold testing. Test results will be printed directly from the immittance device or recorded manually at the conclusion of testing on each ear. Probe tips must be appropriate in size to seal the participant's ear canal tightly during tympanometry and acoustic reflex testing. Clinical centers must have an adequate variety of sizes of probe tips to accommodate ear canals of varying dimensions.

5.11.3 Audiometer

Audiometers that meet the American National Standard Specifications for Audiometers [1] and have two channels are used to conduct pure tone air and bone conduction threshold, SRT and word recognition testing. One channel of the audiometer generates and delivers the test signals, either pure-tones or prerecorded speech. The second channel delivers narrow-band or speech-band masking noise simultaneously with the test signal, but to the non-test ear whenever necessary. The audiometer must have an input jack for external equipment such as a compact disc player or tape player, which will be used to present speech stimuli for word recognition testing.

5.11.4 Audiometer Transducers

Earphones mounted in supra-aural cushions and calibrated according to the American National Standard Specification for Audiometers [1] are used to deliver the test material from the audiometer to the participant. The earphones are designated as "right" and "left" and will be placed comfortably over the participant's right and left ears, respectively. Bone vibrators calibrated according to the same standards are used to obtain bone conduction thresholds. During the testing, the bone vibrator is positioned over the mastoid area of the participant's test ear, taking care that it is not in contact with the posterior part of the pinna.

5.11.5 Compact Disc Player

A compact disc player must be used to deliver pre-recorded speech material to the audiometer and subsequently to the transducers positioned over the participant's ears. A cable extends between the output jack of the compact disc player and the input jack of the audiometer.

5.11.6 Distortion Product Otoacoustic Emissions System

There are no standards for DPOAE equipment. Each study site will use their clinical DPOAE system to accomplish testing as specified in the protocol.

5.11.7 Auditory Brainstem Response

There are no standards for ABR equipment. Each study site will conduct ABR testing according to their standard clinical protocol to rule out the presence of retrocochlear pathology.

5.11.8 Maintenance

Each clinical center is responsible for the proper operation and maintenance of its audiometric equipment. Responsibility for proper maintenance is assumed by the Lead Audiologist, and all staff are instructed to report promptly any real or suspected equipment problems to that person. All checks, inspections, and repairs are documented and recorded by date in a permanent log. The Study Chair and Study Senior Audiologist may review this log at periodic site visits. All study test equipment including audiometers and acoustic immittance devices must be calibrated according to the American National Standards Institute. Listening checks may help to identify problems that could influence participants' test behavior and audiometric results in between scheduled physical calibrations. Study audiologists should perform a listening check on any day when a participant enrolled in the protocol will be tested.

5.12 REFERENCES

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CHAPTER 6
PARTICIPANT ELIGIBILITY AND SCREENING

6.1 OVERVIEW

The first official study visit is the screening or baseline visit (Visit #1.0). However, it is likely that clinic staff will become aware of potential participants in the daily course of clinic operation. The process of moving participants to and through the official study visits may require some participant encounters before the study visit. Most of the participant eligibility criteria are provided to ensure participant safety. Since these safety issues are standard of care to treat SSNHL participants with steroids, most of this activity will be part of normal patient care management, and as such will not present an additional clinic burden. The first official study data will be collected at the Baseline visit, when eligibility will be confirmed.

It is imperative not to admit ineligible people to the study. If the participant is ineligible and randomized, we must subsequently obtain a protocol exception or withdraw that participant from the study and classify them as a misrandomization. Because of this, considerable care must be taken to ensure the eligibility of potential study participants.

The eligibility will be established at the first official study visit (Screening). As stated above, most eligibility criteria are to protect the participant from adverse effects associated with prednisone or IT treatment. The eligibility criteria associated with the baseline visit are relatively extensive.

6.2 ELIGIBILITY CRITERIA AT THE BASELINE SCREENING VISIT (Visit #1.0)

Data required establishing eligibility at the screening visit will be provided from five sources: 1) audiologic evaluations, 2) *Baseline Participant* form, 3) laboratory results, 4) physician review, and 5) informed consent documents. Because of the number of data sources and the complexity of the criteria, an *SSNHL Eligibility Checklist* (see section 10.3.9) has been developed as a worksheet to assist the clinic staff in summarizing that all of the criteria have been examined and eligibility is assured. As a worksheet, the *SSNHL Eligibility Checklist* will not be entered into the study database; however, data forms from each of the five sources of data required to establish eligibility will be entered. The Data Management Center will thoroughly review the data items on the study forms to verify that only eligible people are admitted to the study. Because of the complexity of the baseline eligibility criteria, without the *SSNHL Eligibility Checklist,* mistakes are likely to be made in screening potential participants for the study. Therefore, the CRC and PI are required to check data using the checklist.

The eligibility criteria required to provide study drug (prednisone or methylprednisolone sodium succinate) at the baseline visit are reviewed below. As these data are collected, the CRC transfers their status to the *SSNHL Eligibility Checklist* that summarizes the data from all sources. With the positive completion of the *SSNHL Eligibility Checklist* the potential participant can be invited to participate in the study (which involves taking oral prednisone for 19 days or having a series of four methylprednisolone injections administered over 14 days).

6.2.1 Eligibility Criteria Based on Audiology

Baseline audiological measures are collected on the *SSNHL Audiology Data* form. Each audiologic evaluation consists of a battery of tests designed with intentional cross checks to highlight SNHL. It is possible to have multiple causes of hearing loss. Therefore, it is necessary

to rule out any other existing conditions that may not be related to SSNHL. Those with other ear problems are excluded from the study (with the exception of chronic symmetric acoustic trauma or presbycusis).

Pure tone air conduction thresholds are the primary audiological measures used to determine eligibility requirements for the trial. These are among the most important data collected for this clinical trial for they will determine trial outcomes. Documentation of these primary measures must reveal the following:

1) Unilateral SNHL with ≥50 dB PTA (from four frequency average of 500, 1000, 2000, and 4000 Hz) in the affected ear.

   Hearing must have been symmetric (by participant self report) prior to onset of the SSNHL. Preexisting binaural symmetric SNHL due to presbycusis or chronic noise-induced hearing loss is NOT an exclusion criterion.

   In many cases an outside audiogram may have been obtained by non-study personnel prior to evaluation by study personnel. The Clinical Site PI is responsible for determining whether the responses from this audiogram will be collected as study data (Baseline audiogram) or a new Baseline audiogram will be obtained by Clinical Site audiologists. In any case, the data will be evaluated and recorded (FORM 3) by the site lead audiologist.

2) The affected ear must be ≥30 dB worse than the unaffected ear in at least one of the four PTA frequencies. This will assure that potential participants with preexisting symmetric SNHL have sufficient interaural asymmetry to reliably detect treatment effect.

3) Though not used to power the study, word recognition scores will be tested at each scheduled audiometry session. This must be tested using full-length recorded lists, as detailed in Chapter 5: Audiology Procedures of this MOP.

6.2.2 Eligibility Criteria Based on Baseline Participant Questionnaire

Data to establish eligibility provided by self report of the potential participant are collected on the *SSNHL Baseline Participant* questionnaire. This questionnaire has a section regarding medication usage, a section regarding allergies, and a detailed "review of systems" section listing possible physical symptoms or complaints. Instructions for completing this form are flexible so that the CRC may query the potential participant for details and refine their responses. For example, when a potential participant reports use of steroids in the past 14 days, the CRC is free to ask for additional information. If after consideration of this additional information the potential participant has clearly not used steroids for more than 10 of the past 14 days, this answer should be indicated.

Many criteria are self explanatory, such as the exclusion of those with age less than 18. Others require the clinical judgment of the CRC. Where these issues exist, it is the responsibility of the CRC to inform the Clinical Site PI, and, in cooperation with the PI, establish eligibility. Each criterion is briefly discussed below:

<u>Inclusion criteria</u>

1) *Male and female participant's ≥18 years of age in good health*
2) *Unilateral SNHL developing within 72 hours*
3) *Pure tone average ≥50 dB:* PTA is calculated from thresholds at four frequencies (500, 1000, 2000, and 4000 Hz) in the affected ear, with the affected ear ≥30 dB worse than the contralateral ear in at least one of the four PTA frequencies
4) *Symmetric hearing prior to onset of SSNHL:* To the best of the potential participant's knowledge, hearing prior to onset of the SSNHL was symmetric.
5) *New hearing loss is idiopathic:* Hearing loss must be determined to be idiopathic following an evaluation by an otolaryngologist, appropriate blood tests, and imaging studies.
6) *Preexisting symmetric SNHL is not necessarily an exclusion criterion:* potential participants may be enrolled if they have preexistent symmetric SNHL due to presbycusis or preexisting chronic noise-induced hearing loss, provided that a new unilateral hearing loss meeting criteria 2 and 3 (above) is present.
7) *Duration of SSNHL ≤14 days:* Participant enrollment must be accomplished within 14 days of SSNHL onset.
8) *Pre-enrollment steroid usage for <10 days:* Participants may be enrolled if they have already begun oral steroid treatment for their SSNHL, as long as that treatment has been for a total duration of less than 10 days, regardless of dose.
9) *English or Spanish language competency required:* Participants must be able to read or write English or Spanish. They must be able to repeat words in English or Spanish so that word identification tests can be conducted.

Exclusion criteria for systemic disease

The following conditions or situations would contraindicate entry into this study because there would be significant risk of ascertainment (misclassification) bias regarding the correct diagnosis of idiopathic SSNHL or because of significant risk from their disease if such participants were given immunosuppressive drugs. Whether or not the potential participant meets criteria will be determined by the PI at each site.

1) *>10 days prior oral steroid treatment for any reason within the preceding 30 days*
2) *Tuberculosis:* History of tuberculosis or of prophylactic tuberculosis therapy for positive skin test (PPD)
3) *Insulin-dependent diabetes:* Diabetes mellitus may substantially increase the risk of oral steroid usage.
4) *History of rheumatic disease:* Rheumatic disease, including rheumatoid arthritis, scleroderma, lupus erythematosus, polymyalgia rheumatica, polyarteritis nodosa, temporal/giant cell arteritis, Sjögren's syndrome, or ulcerative colitis, may complicate use of oral steroids. Such participants may have other causes of SSNHL that could be a confounding variable (diagnostic misclassification).
5) *Active atherosclerotic vascular disease:* History of unstable angina, coronary artery stenting or bypass grafting within 3 months of enrollment, transient ischemic attacks or stroke within 4 weeks of enrollment, or cardiac arrhythmia could cause sudden deafness by other mechanisms than those under study,

producing diagnostic misclassification.

6) *Serious psychiatric disease:* Serious psychiatric disease or history of psychiatric reaction to corticosteroids could substantially increase risk of participation in oral steroid therapy.
7) *Prior treatment with chemotherapy agents, immunosuppressive drugs:* Use of chemotherapy and/or immunosuppressant agents, such as azothioprine, cyclophosphamide, leukoran, or other alkylating agents, or cyclosporine, FK506, etanercept, infliximab, or interferon, may alter the SSNHL disease process, alter response to the treatments of the SSNHL study, or increase risk of using the study drugs.
8) *Pancreatitis:* Pancreatitis can substantially increase risk of using oral steroids.
9) *Active peptic ulcer disease or history of GI bleeding:* Active peptic ulcers or history of GI bleeding can substantially increase risk of using oral steroids.
10) *History of known HIV, hepatitis C, or hepatitis B infection:* These conditions could be activated or worsened by use of the study medications.
11) *Chronic renal insufficiency:* Chronic renal insufficiency requiring dialysis can alter metabolism of the study drugs, substantially increasing risk of their use.
12) *Alcohol abuse:* Alcohol abuse can alter metabolism of the study drugs, substantially increasing risk of their use.
13) *Active shingles (herpes zoster infection):* Shingles could be activated or worsened by use of the study medications.
14) *Severe osteoporosis:* Advanced/severe osteoporosis or nonsurgical (mild) aseptic necrosis of the hip could be activated or worsened by use of the study medications.
15) *General anesthetic:* General anesthesia could be associated with other significant medical problems and could also induce fluctuations in blood pressure, pulse, or blood coagulation that could lead to other causes of SSNHL.
16) *Head and/or neck radiation therapy*: Both head and neck cancer and radiation therapy could induce other causes of SSNHL.

Exclusion Criteria for Otologic Disease:

The following conditions or situations would contraindicate entry into this study because of the significant possibility that they could cause SSNHL, resulting in ascertainment bias regarding the correct diagnosis of idiopathic SSNHL as defined herein.

1) *History of previous or recurrent unilateral SSNHL*
2) *History of fluctuating hearing in either ear*
3) *History of Meniere's syndrome in either ear*
4) *History of chronic granulomatous or suppurative otitis media or cholesteatoma in either ear*
5) *History of otosclerosis in either ear*
6) *History of prior ear surgery of any kind (except ventilating tubes)*
7) *Asymmetric SNHL prior to onset of SSNHL*
8) *Any congenital hearing loss, even if symmetric or conductive*
9) *History of blunt or penetrating ear trauma, barotrauma, or acoustic trauma immediately preceding SSNHL*
10) *History of luetic deafness [1*

11) *History of genetic SNHL with strong family history*
12) *Craniofacial anomalies or known temporal bone malformations as revealed by CT scan*

6.2.3 Eligibility Based on Laboratory Measures

Among the eligibility requirements for the study, obtaining and checking laboratory results could possibly slow the processing of the potential participants to the study. However, these laboratory assays were chosen to ensure participant safety. All baseline lab work must be drawn (but not confirmed) before administration of any study drug. Because local laboratories will be used for establishing these values, it was felt that all the actual values resulting from the assay are not of interest to the study (local variations in techniques would lower the value of pooled data). As such, the study requirements involve reviewing tests results and recording individual results as normal/abnormal. If abnormalities are reported then the lab value will also be recorded. Required lab work for baseline eligibility include hematocrit, white blood count, blood glucose, urinalysis, and imaging and/or brainstem auditory evoked response to rule out retrocochlear disease. Pregnancy test is recommended if indicated for women of child-bearing age. All other lab work will be obtained at the discretion of the Clinical Site PI, based upon his/her clinical assessment and the participant's self report of medical history, and the resulting values thoroughly reviewed before providing study drug. The study results will be recorded on the *SSNHL Baseline Laboratory Measures* form. Assays obtained and details of individual tests follow below:

1) *HCT and WBC:* hematocrit and leukocyte count should be within normal limits; any abnormalities should be evaluated.
2) *Urinalysis*: protein, blood, and microscopic hematuria should be within normal limits; any abnormalities should be evaluated.
3) *Other tests if indicated*:
   - Liver function tests: alkaline phosphatase, ALT, AST, bilirubin (direct and total), LDH, protein (albumin and total), renal function tests: BUN and creatinine
   - PPD for question of tuberculosis exposure
   - Hepatitis screen
   - Syphilis screen
   - Immunologic studies: ANA, rheumatoid factor, ANCA, LE prep, Complement levels, ESR, other immune studies
   - HIV test
   - Lyme titre
   - Chest x-ray
   - Electrocardiogram and/or other cardiac function tests
   - Other tests

The *SSNHL Baseline Laboratory Measures* form is described in Chapter 10.

6.2.4 Eligibility Criteria Based on Physician

Data to establish eligibility will also be collected on the *SSNHL Baseline Physician* form. Like the *SSNHL Baseline Participant* form, the Clinical Site PI is encouraged to

both probe with questions and use appropriate additional tests (as required) to establish the eligibility of the potential participant. As examples, the Clinical Site PI should probe for additional information to confirm a positive report of steroid use, and should obtain an MRI or CT to confirm suspected craniofacial or temporal bone developmental abnormalities. The goal of the eligibility questions on the *SSNHL Baseline Physician* form is to ensure the selection of appropriate participants that the study drugs can safely treat. Details of individual items are below:

1) *Cochlear otosclerosis*: Radiographic exam should confirm suspected cochlear otosclerosis.
2) *Autoimmune inner ear disease:* One or more months of rapidly progressive deafness usually affecting both ears.
3) *Cogan syndrome*: Ophthalmologic exam should confirm suspected Cogan syndrome or atypical Cogan syndrome.
4) *Perilymph fistula, or middle ear or ossicular reconstruction*
5) *Genetic SNHL with strong family history*
6) *Chronic suppurative otitis media*
7) *Craniofacial or temporal bone developmental anomalies*: Abnormalities detected or suspected on physical exam should be confirmed by CT or MRI as appropriate.
8) *Unstable or brittle diabetes*
9) *Evidence of current shingles (herpes zoster)*: Laboratory assessment and/or chart review should confirm cases of suspected shingles.
10) *Ability to participate in the SSNHL study/Ability to comprehend and speak English or Spanish*: If there is a reason the investigator does not feel that the participant will complete the study protocol (including an inability to speak the languages used in hearing assessment), the PI is able to exclude the potential participant.
11) *Any corticosteroid use for more than 10 days within the last month*: A positive report of steroid use should be followed by queries to establish the type of steroids. It is possible that the potential participant will misreport steroid use, and before providing a positive history the Clinical Site PI should attempt to confirm such use.

6.2.5 Eligibility Requirements based on Presence of Informed Consent

The presence of true informed consent, with the full understanding of the study requirements and risks by the potential participant, is a central moral and practical issue to any clinical trial. As such, the potential participant must understand and sign the informed consent before receiving study drug.

6.2.6 Eligibility Checklist

Questions involving eligibility have been shaded on the *Baseline Visit* forms to highlight potential problems during the screening process. The *Eligibility Checklist* summarizes these questions by their source as a guide to confirming eligibility. See Chapter 10 for examples of baseline forms.

6.3 Reference

1) Darmstadt GL, Harris JP. Luetic hearing loss: clinical presentation, diagnosis, and treatment. Am J Otolaryngol 1989;10(6):410-21.

CHAPTER 7

BASELINE VISIT

7.1 OVERVIEW

The baseline visit will generally consist of two parts, eligibility screening (Visit #1.0) and enrollment (Visit #2.0). Each new potential participant will be assigned a screening number. Eligibility screening is described in detail in Chapter 6, and will consist of completion of:

1) Informed Consent and HIPAA form
2) *Audiology Data* form
3) *Audiology Eligibility* form
4) *SSNHL Baseline Participant* questionnaire
5) *SSNHL Baseline Physician* form
6) *SSNHL Baseline Laboratory Measures* form
7) *Retrocochlear Rule Out* form
8) *SSNHL Eligibility Checklist* form

Those individuals who are deemed eligible for the study after completing the eligibility screening will be invited to participate in the study. In most cases, participants will be informed of the study and enrolled at the time of their initial clinic visit.

At the time of enrollment the participant will:

1) Undergo randomization to treatment assignment
2) Receive verbal and written patient education material about the possible side effects of the study drugs (prednisone and methylprednisolone), precautions while taking the medications, instructions on the dosage schedule, and know who to contact in the event of an emergency
3) Initiate treatment

Participants will then be given a 19-day supply (14-day treatment, plus five-day taper) of prednisone or receive the first of four methylprednisolone injections. At this time the CRC will review the study protocol with the participant and schedule the remaining study visits.

7.2 SIGNING THE INFORMED CONSENT FORM

At the beginning of the baseline visit, the potential participant will have an opportunity to review the consent form and have all questions answered. During this discussion, every effort will be made to inform the potential participant fully of all aspects of the trial, including the potential risks, benefits, time demand, and follow-up procedures. Their full understanding of the overall trial is important for ethical considerations as well as for compliance with the study design.

Every clinical trial's success depends on the cooperative effort of its participants. Participants must take the study drug as prescribed, complete a variety of questionnaires about health and medical history, have an otologic exam, and audiometric testing, and safety monitoring laboratory tests, return for follow-up visits as indicated, and report any symptoms or adverse effects that may develop.

It should be stressed that the SSNHL study will not be providing primary medical care to the participants. They will continue to go to their usual source of medical care throughout the course of the study.

Refer to Chapter 4: Informed Consent Guidelines for detailed instructions about obtaining informed consent. The consent forms will be maintained at each Clinical Site until the end of the study.

7.3 INSTRUCTIONS FOR COMPLETION OF SSNHL SCREENING AND ELIGIBILITY FORMS

As detailed in Chapter 6, eligibility screening is based on data collected on five SSNHL forms:

1) *Audiology Eligibility* form
2) *SSNHL Baseline Participant* questionnaire
3) *SSNHL Baseline Physician* form
4) *SSNHL Laboratory Measures* form
5) *SSNHL Eligibility Checklist*

7.3.1 Audiology Eligibility Form

The *SSNHL Audiology Eligibility* form is completed by the Lead Audiologist and reviewed by the CRC to be sure all data are present and that the potential participant meets audiometric eligibility criteria as detailed in Chapter 6.

7.3.2 Baseline Participant Questionnaire

The *SSNHL Baseline Participant* questionnaire has three general areas of information, medication usage, allergies, and review of systems. The medication section is completed by the CRC by interviewing the potential participant. This section is used to gather information about all prescription medicines used during the one-month period prior to this interview, as well as recent or regular use of selected over-the-counter medications and supplements. The potential participants list all medications and the clinic staff should review this information with them and examine the medications they bring in to make sure they are recorded accurately. After the information is recorded, the interviewer probes the potential participant about each prescription medicine for any additional information and also asks several questions regarding use of over-the-counter medications and supplements.

The definition of a prescription medication is a medication for which a prescription was written by a physician, dispensed by a physician or pharmacist, and taken during the one month period prior to the interview. This includes prescriptions for eye drops, pills, tablets, or capsules, creams/salves/ointments, dermal patches, and “injectables” (allergy shots/insulin).

Nonprescription medications are defined as medications that may be purchased without a physician prescription.

If the potential participant forgot to bring medications to the baseline visit, each Clinical Site is responsible for developing a mechanism to obtain this information. The allergy section of this form is self-explanatory and deals with medication and latex allergies.

The symptoms checklist, or “review of systems”, is a detailed list of symptoms and complaints that prompt the potential participant to reveal and discuss any ongoing medical issues they may have.

7.3.3 Baseline Physician Form

The *Baseline Physician* form has sections that review diagnostic eligibility criteria, clinical exclusion criteria, detailed otologic and vestibular review of systems, and general, otologic and neurologic physical exam. The form is completed by the Clinical Site PI based upon interview and physical examination of the potential participant.

7.3.4 Baseline Laboratory Measures Form

The *Baseline Laboratory Measures* form includes required lab values for hematocrit, white blood count, serum glucose, and urinalysis. It also includes any other laboratory values obtained at the discretion of the clinic physician. All participants are requested/invited to donate one additional redtop tube of blood for future immunological studies of SSNHL (see MOP Chapter 9). Status of this donation request is noted on this form. Subjects may "opt out' of this donation on the *Informed Consent* form without otherwise affecting their participation in the study.

7.3.5 Eligibility Checklist

The *Eligibility Checklist* is a tabulation of information from the preceding four forms, using shading to denote all critical values that enter into the eligibility determination. Subjects who meet all criteria are eligible for the study and are invited to participate. Those who decline to participate are interviewed by the CRC to complete the appropriate section of this form.

7.4 RANDOMIZATION AND ENROLLMENT PROCESS

7.4.1 Overview

Because at least one study [1] has indicated that subjects with hearing PTA ≥90 dB may not respond as well to treatment as those with less severe hearing loss, we will stratify the randomization on the baseline PTA (50 to <90 vs. ≥90 dB). Subjects will also be stratified by clinical site. A randomization schedule has been computer generated for each of the Clinical Sites using a modified block randomization scheme. The randomization codes will employ a permuted block randomization scheme with each block size a randomly determined multiple of 2 and a maximum block size of six. The randomization assignment and associated code will be developed by the Data Management Center. The six-digit randomization number will be comprised of the three-digit Clinical Site number, and a unique three-digit number beginning with a predetermined number that is associated with the stratified group(PTA) followed by a two-digit random number.

7.4.1.1 Telephone randomization

If the potential participant has signed the informed consent form and qualifies for randomization, then the CRC will be able to randomize them by phoning the Data Management Center. Telephone randomization will be available from 8:00 AM – 4:30 PM central time, Monday-Friday.

The steps to randomize are as follows:

a) Complete Form 93: *Notice of Informed Consent*
b) Fax Form 93 to:

Linda Graham
Data Coordinator, Hines Data Center
Fax #: 708-202-7928

c) To randomize the subject, call Linda Graham at 708-202-5856. If Linda is unavailable, call 708-202-5853 and mention that you wish to randomize a subject for the SSNHL study. You will be transferred to the assigned back-up.

For randomization after 4:30 PM CST (to 7:30 PM CST) or 2:30 PM PST (to 5:30 PM PST) call Nancy Ellis at 262-271-2285. During these hours Nancy Ellis will ask you to verify the last randomized participant at your site.

Personnel will be queried for the required information listed in Form 52:

- Site number (hospital code)
- Participant ID number
- Did the participant sign consent form? Y/N
- Does the participant qualify for randomization? Y/N
- Date of birth MM/DD/YYYY
- Gender M/F
- Baseline PTA in affected ear
- Hearing stratification group (≥90 dB PTA, < 90 dB PTA)
- Days of prior steroid use

After submitting the required information, the participant will be assigned a treatment group (IT or oral) from the stratified randomization list and will be given a randomization number which the CRC will enter in Form 52.

7.5 PARTICIPANT EDUCATION

7.5.1 Possible Side Effects

Prednisone and methylprednisolone are powerful anti-inflammatory agents. They may suppress the immune system if used for long periods of time. Short term use (a few weeks, or less than a month) generally will not affect the immune system. The side effects from these drugs are dose and time related. There is no completely "safe" dose of this drug. Men often tolerate the drug better than women. The high doses of steroids used in this study may produce unwanted effects for the participant, but these must be weighed against the possibility of permanent loss of hearing if the hearing is left untreated. Participants with a history of gastritis or GI intolerance of non-steroidal anti-inflammatory drugs may wish to use an antacid or H2-blocker such as ranitidine to reduce risk of similar steroid side-effects. The participant should be made aware of the following possible side effects:

<u>Minor Side Effects that usually do not require treatment</u>:

Increase in appetite
Weight gain
Indigestion
Nervousness/anxiety
Mild depression
Restlessness

Trouble sleeping
Headache
Increased sweating
Mild infections
Increase in hair growth

Major side effects which the participant should report to the CRC or clinic physician:

Confusion
Excitement
Hallucinations
Paranoia
False sense of well being
Mental depression
Irregular heartbeats
Shortness of breath
Hypertension
Frequent urination
Increased thirst
Rapid weight gain
Edema
Bloody or black tarry stools
Stomach pain or burning
Pain or weakness
Unusual tiredness
Any major infection
Stress fractures
Reddish purple lines on skin
Cataracts

A patient education handout detailing these potential risks and side effects should be distributed to each participant. A copy of this handout is provided in Section 7.8.

7.5.2 Precautions While Using Corticosteroids

Clinic staff should inform the participants of the following precautions when using prednisone:

1) Do not stop taking this medicine without first talking with the Clinical Site PI or CRC. In the event that the participant needs to go off the prednisone, it may need to be reduced gradually.
2) In the event of any surgery or medical emergency, the participant should tell the treating physician that he/she is on prednisone.
3) Participants should talk with the Clinical Site PI or CRC before having any type of immunization, especially with live polio vaccine or skin tests.
4) If the participant has any serious infection or injury, he/she should tell the treating physician that they are taking prednisone.
5) Participants should be told to avoid anyone who has chickenpox or measles. If the participant thinks they have been exposed to chickenpox or measles they

should tell the Clinical Site PI or CRC immediately.

7.5.3 Dosage Schedule

Participants in the oral prednisone treatment group will be given a 19-day supply of prednisone in the form of 10 mg tablets. Participants will take a single daily dose of six 10 mg tablets in the morning each day for the first 14 days, and then taper the dose over 5 days with the following schedule: 50 mg (5 tabs) on day #15, 40 mg (4 tabs) on day #16, 30 mg (3 tabs) on day #17, 20 mg (2 tabs) on day #18, and 10 mg (1 tab) on day #19. This is a total of 99 tablets. The actual prescription will be for 100 tablets in order to provide an extra pill in case one is lost. Participants should be told:

1) If you forget to take your medication in the morning, take it as soon as you remember.
2) If you forget to take your medication for the day, take your *regular* dose the following morning.
3) Never take a double dose of this medication.
4) Always bring your medication bottle to each clinic visit.

This information should also be given in writing to the participant for easy reference.

Participants in the methylprednisolone injection group will receive their first dose on the day of enrollment. The tympanic membrane is anesthetized with topical phenol solution at two sites, anterior and posterior. A needle puncture is made in the anterior site as a vent to release air bubbles during injection. The medication is instilled through the posterior site. These sites typically remain anesthetic for two weeks and do not need to be reanesthetized. A single-use vial containing 500 mg of desiccated preservative-free methylprednisolone sodium succinate (SoluMedrol®) is reconstituted with 12.5 ml of sterile water to a final concentration of 40 mg/ml. The solution is gently warmed to body temperature and injected into the middle ear using a tuberculin syringe and 1.25-in. 27 g needle. The drug solution is instilled to a total volume of 1 ml or until the middle ear is filled and the solution begins to flow out of the vent hole in the anterior tympanic membrane. The participant remains supine for 30 minutes and is then discharged on water precautions.

7.6 EMERGENCY CONTACT INFORMATION

The participant should be given information on who to contact in the event of a medical emergency or if they develop any unusual symptoms. Information should include the CRC's daytime phone and the clinic number for days and evenings. Participants should also be given instructions on what to do if they cannot reach the Clinical Site PI. If the Clinical Site PI has other physicians or clinicians that are on call, they should be briefed in advance about the study.

7.7 SCHEDULING SUBSEQUENT VISITS

Prior to the participant leaving, he/she should be scheduled for all return appointments. Subjects in the IT methylprednisolone group will return at 3-4 day intervals for a total of four doses in 14 days. All participants will have a follow-up visit in two months and a late follow-up visit in six months (see CRC Flowchart, section 7.9).

7.8 PATIENT EDUCATION HANDOUT

This is a sample of the patient education handout on use and risks of corticosteroids:

STEROID THERAPY: PATIENT INSTRUCTIONS

GENERAL INFORMATION

1. Steroid therapy is being given to you as treatment for your hearing loss. Steroids are powerful anti-inflammatory agents.

2. Steroid therapy requires careful administration and monitoring. You will need to the see the doctor at the beginning of treatment and again in 1 week and 2 weeks. The duration of therapy varies for different conditions. In this study of Sudden Sensorineural Hearing Loss (SSNHL) the treatment is for 2 weeks.

3. Pulse rate, blood pressure, blood sugar, and urinalysis are checked when you begin prednisone treatment and again in 1 week.

4. Oral steroid therapy will be taken DAILY as prescribed. The total dose should be taken all at once, at the same time each morning. If you forget to take your pills in the morning, take it as soon as you remember that same day. Resume the usual time and dose of prednisone the next day. If you miss a dose and don't remember until the following day, do NOT take a double dose of prednisone – just take the usual daily dose only. If more than one day of oral steroid therapy is missed, call your Clinic Doctor or Clinical Research Coordinator immediately.

Steroid injection therapy will be administered every 3-4 days according to a schedule assigned by your doctor. If you must miss a scheduled appointment, contact the Clinical Research Coordinator as soon as possible to arrange an alternate injection visit. Likewise, if you forget a scheduled injection appointment, contact the Clinical Research Coordinator as soon as possible to reschedule a visit.

5. Steroids may lead to thinning of your bones (osteoporosis). Calcium (1500 mg/day) and Vitamin D (400 IU/day) supplements are recommended to minimize this risk.

6. Steroids may cause stomach irritation, ulcers, or bleeding in the stomach or intestines. Preventive medicine to avoid these problems will be prescribed by your Clinic Doctor.

POTENTIAL SIDE EFFECTS:

Minor Side Effects – usually NOT requiring treatment

Increased appetite	Weight gain	Indigestion
Nervousness	Trouble sleeping	Depression
Headache	Restlessness	Anxiety
Increased sweating	Mild infections	Increased hair growth

Major Side Effects – SHOULD be reported to Clinic Doctor or Clinical Research Coordinator

Confusion	Excitement	Hallucinations
Paranoia	False sense of well-being	Severe depression

Edema/swelling	Bloody/black stools	Rapid weight gain
Stomach pain/burning	Irregular heartbeat	Frequent urination
High blood pressure	Increased thirst	Shortness of breath
Unusual tiredness	Red/purple lines on skin	General pain or weakness
Cataracts	Stress fractures	Any major infection

PRECAUTIONS:

1. Do NOT stop taking oral steroids without first talking with Clinic Doctor or Clinical Research Coordinator; termination of treatment needs supervision.

2. In the event of any surgery, medical emergency, serious infection, or injury, tell the doctor/surgeon that you are taking steroids.

3. Speak to the Clinic Doctor or Clinical Research Coordinator before having any skin tests or immunizations (vaccines), especially live polio or smallpox vaccine.

4. Avoid contact with anyone who has chickenpox or measles. Contact the Clinic Doctor or Clinical Research Coordinator immediately if exposure occurs.

CONTACT SOURCES:
If you have any questions or concerns, please call your
Clinic Doctor _____ at Tel: _____, or
Clinical Research Coordinator _____ at Tel: _____.

7.9 Clinical Research Coordinator Flowchart

CRC FLOWCHART SUBJECT ID_____ SUBJECT INITIALS_____

1.0 SCREENING
Date_____
___Informed Consent/HIPAA (Form 93)
___Audio Data (Form 3)
___Audio Eligibility (Form 4)
___Baseline Participant (Form 5)
___Baseline Physician (Form 2)
___Baseline Lab Measures (Form 6)
___Eligibility Checklist (Form 1)
___Self-Report (Form 0)
___Retrocochlear R/O (Form 7)
Sent:_____ Rec'd_____
___Contact Information (Form S1)

2.0 BASELINE VISIT
ENROLL/RANDOMIZE:
TREATMENT #1
Date:_____

___Randomization Form (Form 52)
___Pain Scale (Form 8)
___Treatment (Oral:Form 9; IT:Form10)
___AE Form (Form 50)

3.0 IT TREATMENT #2
Date_____
___IT Treatment (Form 10)
___Pain Scale (Form 8)
___AE Form (Form 50)
___Phone Call (Oral)
___Pain Scale ___AE Form

4.0 IT TREATMENT #3
/ORAL CHECK-UP
Date_____
___IT or Oral Treatment (Oral: Form9; IT: Form 10)
___Pain Scale (Form 8)
___Weekly Lab (Form 11)
Sent_____ Rec'd:_____
___AE Form (Form 50)

___Audio Data (Form 3)
___Physician F/U Questionnaire
___CRC F/U Worksheet

5.0 IT TREATMENT #4
Date_____
___IT Treatment (Form 10)
___Pain Scale (Form 8)
___AE Form (Form 50)
___Phone Call (Oral)
___Pain Scale (Form 8)
___AE Form (Form 50)

6.0 IT POST TREATMENT
/ORAL TAPER
Date_____
___Oral Treatment (Form 9)
___Pain Scale (Form 8)
___Weekly Lab (Form 11)
Sent:_____ Rec'd____
___AE Form (Form 50)
___Audio Data (Form 3)

___Patient Education Handouts
___Physician F/U Questionnaire
___CRC F/U Worksheet

7.0 FOLLOW-UP 1:
Date_____
___Oral Treatment (Form 9)
___Pain Scale (Form 8)
___Weekly Lab (Form 11)
Sent: _____ Rec'd:_____
___AE Form (Form 50)
___Audio Data (Form 3)
___Physician F/U Questionnaire
___CRC F/U Worksheet

8.0 FOLLOW-UP 2:
Date _____
___Pain Scale (Form 8)
___Weekly Lab (Form 11)
Sent:_____ Rec'd_____
___Audio Data (Form 3)
___AE Form (Form 50)
___Physician F/U Questionnaire
___CRC F/U Worksheet
___End of Follow-Up (Form 53)

COMMENTS:_____

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CHAPTER 8

TREATMENT AND FOLLOW-UP VISITS

8.1 OVERVIEW

The main purpose of the treatment visits and subsequent two follow-up visits is to administer the study treatments, monitor participant's safety, and assess the impact that the treatments have on the participant's hearing. At each visit participants will be evaluated for possible adverse events (AEs). Prior to this clinic visit, the CRC can phone participants or send postcards to remind them of the date and time of their visit. If the participant is in the oral treatment arm of the study, they will be reminded to bring their bottle of prednisone with all remaining medication to the clinic so that a compliance assessment can be done.

8.2 TREATMENT VISITS

8.2.1 Oral Prednisone Treatment Visits (Visits #2.0, 4.0, and 6.0)

Participants randomized to the oral prednisone arm of the study will be given their study drug on the day of enrollment/randomization (Visit #2.0). They will return one week later for Visit #4.0. At each visit, they will be instructed to bring their treatment medications with them. The CRC will examine their study medication bottle for a pill count to assess treatment compliance. During their visits they will be queried about ear pain, new or altered health symptoms and problems, AEs, and an interval history of nonstudy medication usage will be taken. Their blood pressure, pulse rate, and body weight will be measured and recorded. Also, they will have an otologic and focused neurological exam at each visit, while an audiogram and safety monitoring laboratory measures will be completed at specified visits. For type II diabetic participants serum glucose and urinalysis will be checked at least twice weekly. This additional monitoring may be conducted by the study site or by the participant's PCP.

Data forms required at these visits include:

1) *Audiology Data* (Visits #4.0 and 6.0 only)
2) *Pain Scale*
3) *Oral Treatment*
4) *Adverse Events*
5) *Weekly Laboratory* (Visits #4.0 and 6.0 only)

After completion of each examination/interview, the participant will be reminded of their schedule for subsequent visits. For this study arm, this includes a visit in one week (two weeks after randomization-Visit #6.0) during which they will be approximately at the beginning of their five-day drug taper. At this visit all the interviews, examinations, and data forms described above will be repeated. The participant will then appear for two subsequent follow-up visits, at two months (Visit #7.0) and six months after enrollment (Visit #8.0).

Midway through the first and second weeks of treatment (Visits #3.0 and 5.0), the participant will be contacted by telephone for a "telephone visit." During the telephone contact the CRC will query the participant in order to complete the *Pain Scale* and the *Adverse Event* forms.

8.2.2 IT Methylprednisolone Treatment Visits (Visits #2.0, 3.0, 4.0, 5.0, and 6.0)

Participants randomized to the IT methylprednisolone arm of the study will be given their first dose of study drug on the day of enrollment/randomization (Visit #2.0). They will return 3-4 days later for their next treatment Visit #3.0. They will make a treatment visit every 3-4 days until they have received a total of four treatment doses over a two-week interval. During each visit they will be queried about pain, new or altered health symptoms and problems, AEs, and an interval history of nonstudy medication usage will be taken. At Visits #2.0, 4.0, and 6.0 blood pressure, pulse rate, and body weight will be measured and recorded. Also, they will have an otologic and focused neurological exam at each visit, while an audiogram and safety monitoring laboratory measures will be completed at specified visits. The CRC will monitor their compliance with the treatment protocol.

Data forms required at these visits include:

1) *Audiology Data (Visits #4.0 and 6.0 only)*
2) *Pain Scale*
3) *IT Treatment (Visits #2.0, 3.0, 4.0, and 5.0 only)*
4) *Adverse Event*
5) *Weekly Laboratory* (Visits #4.0 and 6.0 only)

After completion of each visit, the participant will be reminded of their schedule for subsequent visits. For participants in this study arm, a return visit will occur every 3-4 days until all four doses have been administered, and then a visit two weeks after initiation of therapy (Visit #6.0) to document their status at completion of their treatment course. At each of these visits all the interviews, examinations, and data forms described above will be repeated. The participants will then return for two subsequent follow-up visits, at two months (Visit #7.0) and six months after enrollment (Visit #8.0).

8.3 FOLLOW-UP VISITS (Visits #7.0 and 8.0)

All participants in the study have the same schedule of follow-up visits, regardless of whether they are randomized to receive oral prednisone or IT methylprednisolone treatment. They have two follow-up visits at two months and six months after enrollment. The purpose of these visits is to assess the primary and secondary outcome measures of the study, including hearing improvement, hearing stability, and the presence of any persistent or late-onset adverse events or side effects of the treatments. At each of these visits the participants will be queried about ear pain, new or altered health symptoms and problems, AEs, and an interval history of nonstudy medication usage will be taken. Blood pressure, pulse rate, and body weight will be measured and recorded. Also, they will have safety monitoring laboratory measures, an audiogram and a focused neurological exam. Visit #7 must occur within one week on either side of the target due date. Visit #8 must occur within two weeks on either side of the target date. Any date outside of the range for visit #7 and #8 will require a protocol exception (Form 56).

Data forms required at these visits include:

1) *Audiology Data*
2) *Pain Scale*
3) *IT Treatment*
4) *Adverse Event*
5) *Weekly Laboratory*
6) *End of Follow-Up*

CHAPTER 9
PHARMACY AND LABORATORY PROCEDURES

9.1 OVERVIEW

Participants in the study are randomized to receive treatment with either oral prednisone or IT methylprednisolone. Dosages and schedules of these treatments are detailed below as well as in Chapter 1 of this MOP. Performance objectives for this study include monitored and safe administration of the study drugs to the participants. This chapter describes the protocol for providing the study drugs to the participants.

Participants in the study are scheduled to undergo a series of safety monitoring laboratory measures on blood and urine. They are also invited to donate one additional red top tube of blood for future immunological studies of SSNHL. This chapter describes the protocol for acquiring and handling these laboratory samples.

9.2 PHARMACY PROCEDURES

9.2.1 Oral Prednisone

Oral prednisone is considered "standard care" for treatment of SSNHL. As such, it is widely available in all hospital and commercial pharmacies. Participants randomized to the oral prednisone arm of the study are to take 60 mg/day for 14 days, followed by a five-day taper on a schedule of 50 mg, 40 mg, 30 mg, 20 mg, and 10 mg for a total of 19 days of therapy. The prednisone will be provided in a bottle of 10-mg tablets. Ninety-nine tablets are mandated by the treatment schedule. The provided bottle should contain 100 tablets; the extra tablet being available for dropped, damaged or lost pills. Local hospital pharmacy routines will differ between Clinical Sites. The participants may either be given the actual bottle of prednisone tablets or they may be given a prescription to fill, in which case they must return to the clinic after filling the prescription in order that the CRC can confirm that the participant has their medication and can commence treatment. Details of prednisone distribution and utilization will be tracked in an *Oral Prednisone Distribution Log* (described below, see section 9.2.2.1).

9.2.2 IT Methylprednisolone

9.2.2.1 Methylprednisolone acquisition and distribution

Use of intratympanic methylprednisolone sodium succinate (Solu-Medrol®) for treatment of SSNHL is experimental and constitutes an "off-label" use of the drug. The Study Chair has applied for and received an Investigational New Drug (IND) approval from the U.S. Food and Drug Administration (FDA) entitling use of the drug in this fashion for purposes of the SSNHL study. Each Clinical Site PI must register with the Study Chair's Office by submitting a completed and signed Form FDA 1572 listing all personnel dispensing the drug. Pfizer Pharmaceutical has also agreed to this experimental use of their product. However, Pfizer has no proprietary role in the design, execution, or outcome of the SSNHL study; they are selling the drug to the study just as they would to any licensed pharmacy.

Prior to the initial distribution of the drug, each Clinical Site must submit to the Senior CRC copies of the letter of approval from their IRB and date-stamped consent form. Throughout the project, the Senior CRC will monitor the status of

IRB approvals before dispensing additional supplies of the drug.

The entire projected supply of drug for the study has been purchased by the Study Chair's Office at the Massachusetts Eye & Ear Infirmary (MEEI) and stored in their clinical pharmacy. An initial distribution of 40 vials (enough for 10 research participants) will be distributed to each Clinical Site. As needed, each Clinical Site will requisition the MEEI Pharmacy for additional supply of drug. Each participating Clinical Site is responsible for developing local routines for drug storage use. Contact information for personnel responsible for drug ordering, distribution, and tracking at each participating Clinical Site will be updated and kept by the Senior CRC. All methylprednisolone shipped from the Study Chair's Office will be logged in both a *Methylprednisolone Distribution Log* maintained by the CRC and a *Methylprednisolone Pharmacy Distribution Log* maintained by the Pharmacist at the MEEI (section 9.5). These logs will record date of shipment, recipient site, quantity, lot number, FedEx tracking number, and date received. In addition, a *Methylprednisolone Receiving Log* will be maintained at each Clinical Site, noting date requested, date received, quantity, lot number, and date each vial is used. Quarterly comparison of the Study Chair's Office log and Clinical Site logs will ensure accurate accounting of all study medication. The following is a list of all drug tracking logs (examples in section 9.5):

1) IT Methylprednisolone Distribution Log (Study Chair's Office, MEEI):

This log will be maintained by the Senior CRC at the MEEI which is the distribution center for the methylprednisolone. The log consists of 12 columns of information: (1) box #, (2) date sent, (3) receiving site, (4) amount sent, (5) total (640 start), (6) Federal Express #, (7) f/u call date, (8) medication received – yes, (9) medication received, (10) amount received , (11) comment, (12) completed by.

2) IT Methylprednisolone Distribution Pharmacy Log (Pharmacy, MEEI):

This log will be maintained by the Pharmacist at the MEEI. The log will consist of seven columns of information: (1) box #, (2) date boxed, (3) lot # (4) expiration date, (5) amount boxed, (6) total (640) start, (7) RPh initials.

3) IT Methylprednisolone Receiving Log (Clinical Site):

This log will be maintained by the Pharmacist at the receiving Clinical Site. The log will consist of four columns of information: (1) date received, (2) amount received, (3) comment, (4) RPh initials.

4) IT Methylprednisolone Administration Log:

This log will be maintained by the CRC at each site. The log will consist of nine columns of information: (1) participant ID, (2) participant initials, (3) date administered, (4) reconstituted by, (5) amount used, (6) amount discarded, (7) administered by, (8) comment, (9) completed by.

5) Oral Prednisone Distribution Log:

This log will be maintained by the CRC at each site. The log will consist of 11 columns of information: (1) participant ID, (2) participant initials, (3) date, (4) pills, (5) script, initial pill count, (6) instructions reviewed, (7) participant

compliance at conclusion, (8) end pill count, (9) comment, (10) completed by.

9.2.2.2 **Methylprednisolone dosage and administration**

Participants randomized to the IT methylprednisolone arm of the study will receive preservative-free methylprednisolone sodium succinate (Solu-Medrol®) 40 mg/ml solution. The drug is supplied in single-use vials containing 500 mg of powdered methylprednisolone. As each participant is due for a dose of IT methylprednisolone, a fresh vial will be reconstituted with 12.5 ml of preservative-free sterile water to a final concentration of 40 mg/ml, and administered according to study protocol (see MOP Chapter 8). One ml of drug solution is required for each treatment. The remainder of reconstituted methylprednisolone in each vial will be discarded. As each vial is used, it will be noted in the Drug Log.

9.3 STUDY PHARMACY CONTACT INFORMATION

(See Appendix A)

9.4 LABORATORY PROCEDURES

9.4.1 Urine Samples

Urine samples are taken at the time of eligibility screening/enrollment (Visit #1.0, 2.0) and again at several treatment and follow-up visits (Visits #4.0, 6.0, 7.0, 8.0). Additional specimens may be acquired at unscheduled visits as deemed appropriate by the Clinical Site PI. The urine is subjected to routine urinalysis to monitor for glycosuria, a possible indication of diabetes, and for cells, a possible indication of urinary tract infection. Urine sample acquisition and handling protocols are done in compliance with local standards at each Clinical Site. Specimens may be obtained in the clinic using appropriate supplies and submitted to the local clinical laboratory for analysis and results reporting. Alternatively, participants may be asked to go to the local clinical lab for specimen donation and analysis.

9.4.2 Blood for Safety Monitoring Lab Tests

Blood samples are taken at the time of eligibility screening/enrollment (Visit #1.0, 2.0) and again at several treatment and follow-up visits (Visits #4.0, 6.0, 7.0, 8.0). Additional specimens may be acquired at unscheduled visits as deemed appropriate by the clinic physician. The routine blood samples, a single red top tube for serum glucose and a single purple top tube for WBC and HCT will be drawn and handled according to local Clinical Site routine. Specimens may be acquired by appropriately trained and equipped personnel in the Clinical Site and submitted to the local clinical lab for analysis and results reporting. Alternatively, participants may be sent to the local clinical lab for sample acquisition and processing.

Safety monitoring for type II diabetics: Serum glucose and urinalysis will be checked at least twice weekly. This additional monitoring may be conducted by the Clinical Site or by the participant's PCP.

9.4.3 Blood for Future Immunological Studies

At the time of initial eligibility screening/enrollment (Visits #1.0, 2.0), and prior to initiation of any treatment, participants are invited to donate a single red top tube of blood

which will be stored for future immunological studies of SSNHL. At the present time, the exact nature of these future studies is undefined. Some participants may not wish to make this donation. They are invited to do so, but if they opt not to, this is noted in the appropriate place on their *Informed Consent* form. Opting out of the red top tube donation has no effect on any aspect of the participant's participation in the study.

This blood sample will be drawn according to local Clinical Site's standard practice as noted above in Section 9.3.2. The sample will be processed as follows:

1) The local clinical lab will centrifuge the sample, discard the cell fraction, and retain the serum.
2) The serum sample will be labeled with the participant's site ID# and participant ID# and stored in a freezer at –20 F at each Clinical Site.
3) Serum samples will be shipped in batches by the CRC with assistance from the local clinical laboratory staff. Since this is a human biological sample, it qualifies by both CDC (Center for Disease Control) and OSHA (Occupational Safety and Health Administration) as biohazardous material. It must be handled accordingly. A Shipment Log (section 9.5) will be maintained at each Clinical Site by the CRC.
4) Batch shipments will be sent OVERNIGHT EXPRESS packed in dry ice to the Blood Sample Site address (Appendix A)
5) IMPORTANT: Do NOT send shipment on a day at the end of the week because the specimens may be left sitting on the loading dock all weekend.

9.4.4 Other Studies and Tests

Other blood tests, imaging studies, cardiac tests, etc, may be obtained at the discretion of the local Clinical Site PI. These tests will be obtained according to local standard procedures and the results reported to the Data Management Center on the appropriate forms.

9.5 LOGS

1) IT Methylprednisolone Clinical Coordinating Distribution Center Pharmacy, MEEI
2) IT Methylprednisolone Distribution Log (Clinical Coordinating Center: MEEI)
3) IT Methylprednisolone Receiving Log (Clinical Site)
4) IT Methylprednisolone Administration Log
5) Oral Prednisone Distribution Log
6) SSNHL Serum Sample Shipping Log

Examples of each log are located on the CD in Adobe Acrobat (PDF) format. The files are named: LOG-[log-name].PDF

CHAPTER 10
FORMS

10.1 INTRODUCTION

This chapter briefly describes the forms and worksheets to be used in the collection of official study data. For organizational purposes, the forms have been divided into those completed during the baseline visit, those completed during subsequent visits, and those forms that are filled out as necessary because of special circumstances. A *Visit Table* (section 10.2) is provided that lists all data forms and shows when they must be completed.

Study forms will be supplied to the Clinical Sites. After the forms are completed and reviewed by the CRC, she/he will make a copy of the forms for the participants' records.

The original forms will be mailed to the Data Management Center twice a month. Refer to Chapter 13, Data Management, for procedural details.

All SSNHL study forms should be completed and/or reviewed by qualified Clinical Site PIs, CRCs and Lead Audiologists. To ensure accurate collection of data, the following general procedures should be followed in filling out study forms:

The CRC should provide instructions for participant's questionnaires. CRCs should review and be familiar with these forms in order to explain the procedures to the participant.

Print in **BOLD CAPITAL LETTERS**. Much information is garbled simply by sloppy handwriting. This can result in time lost in data entry.

Print clearly and use a blue pen.

Clearly enter all dates numerically for month, day, and year using leading zeros as necessary. For example: July 5, 2002 would appear as 07 05 2002.

For all items requiring a mark in the appropriate box, place a circle in the box. Do not use a check mark or other mark because they are more difficult to see and may cause errors in keying. If you make a mistake, mark through it with a single red line, record and circle the correct response, and initial and date it.

1) Record all numerical values carefully in the boxes provided, using leading zeros as necessary. In those rare cases where a value is not available, draw a line through the space(s) to indicate that the item is missing intentionally, and write "PM" (Permanently Missing) beside the response.
2) Check all forms immediately after completion to ensure that they are complete and legible throughout. The staff member that completed them should clarify illegible sections. All corrections should be made by marking through the error and writing the correct entry above it. The staff member making the correction should sign her or his initials and date next to the corrected entry. Do not attempt to erase or write over any entry. *Do not use correction fluid*. Certain items will appear on every form; these are explained in detail below.

10.1.1 Form Headers

Each and every study data form has a standardized header. Fields in the header include three-digit *Site Number*, three-digit Participant *ID#*, *Participant Initials*, two-digit *Visit Number*, two-digit *Form Number*, two-digit *Record Number*, and *Date of Visit*.

Site Number

Each Clinical Site is assigned a three-digit site number.

Each Clinical Site should keep a log of every potential participant seen in the clinic (section 10.7). This log consists of four columns of information: 1) the site ID number, 2) a sequential listing of screening ID numbers, 3) the potential participant's name, and 4) the date the participant was assigned the screening ID number.

The Participant's Identification (ID) Number

This three-digit number is assigned by each Clinical Site to any new potential participant and becomes the assigned participant ID number which will be written on all study forms throughout the study. Before beginning the forms, enter the potential participant's name, initials, participant ID number, and the date on the first available row of the logbook. Once the potential participant agrees to enroll in the study, the three-digit *Site ID* number and three-digit *Participant ID* together constitute a unique participant identifier for use throughout the study.

Participant's Initials

Participants are identified by three initials, first, last and middle. If the participant has no middle initial, enter a "dash".

Visit Number

The visit number is a two-digit designation with a decimal point. All scheduled visits are in the format X.0, with X as the scheduled visit number. All scheduled visit numbers, 1.0-8.0, are listed on the *Visit Table* (section 10.2). Any unscheduled visits are numbered with the last scheduled visit number before the decimal point and a sequential numbering of unscheduled visits after the decimal point. For example, if the last scheduled visit was 3.0 and the participant makes two unscheduled visits before their next scheduled visit (4.0), they are numbered 3.1 and 3.2. Unscheduled visits between scheduled visits 4.0 and 5.0 would be numbered sequentially as 4.1, etc.

Form Number and Record Number

These are internal designations made and used by the Data Management Center.

Date of Visit

Month followed by day followed by year must be entered in the appropriate places.

10.1.2 Final Items

Date Form Reviewed

A Clinical Site staff member, usually the CRC, reviews each form for completeness and consistency. Clearly enter the date that the form was reviewed.

Reviewer's Signature

The Clinical Site staff member completing the form signs the form.

10.2 VISIT TABLE

The table (below) lists all study data forms. There are additional worksheets, flowcharts, and other forms that may be used internally at each Clinical Site but are not transmitted to the Data Management Center and do not appear on the *Visit Table*. The list of forms on the *Visit Table* is grouped into those that are completed during the screening and enrollment process, those completed during scheduled treatment and follow-up, and those that are completed as needed. The scheduled visit # is designated across the top of the columns. The forms completed at each visit are marked in the respective columns.

					Start of wk 2		Start of wk 3	2mo	6mo
	VISIT #:	**1.0**	**2.0**	**3.0**	**4.0**	**5.0**	**6.0**	**7.0**	**8.0**
		Screen	**Randomize/ Rx1**	**Rx2**	**Rx3**	**Rx4**			
S1	Contact Info	x							
0	Self Report	x							
93	Notice Informed Consent	x							
1	Eligibility Checklist	x							
2	Baseline Physician (ptI-Clinical exclusions) (ptII-Baseline H+P)	x							
3	Audiology Data	x			x		x	x	x
4	Audiology Eligibility	x							
5	Baseline Participant Q	x							
6	Baseline Lab Measures	x							
7	Retrocochlear R/O	x							
8	Pain Scale		x	x	x	x	x	x	x
52	Randomization		x						
9	Oral Treatment		x		x				
10	IT Treatment		x	x	x	x			
11	Weekly Lab				x		x	x	x
50	Adverse Event		x	x	x	x	x	x	x
51	Serious Adverse Event	as needed	→	→	→	→	→	→	→
53	End of Follow Up	as needed	→	→	→	→	→	→	→
54	Missed Visit	as needed	→	→	→	→	→	→	→
55	Missed Form	as needed	→	→	→	→	→	→	→
56	Protocol Exception	as needed	→	→	→	→	→	→	→
57	Unscheduled Visit	as needed	→	→	→	→	→	→	→
91	Shipping Log	as needed	→	→	→	→	→	→	→
92	Data Change	as needed	→	→	→	→	→	→	→

10.3 SCREENING AND BASELINE FORMS (Visits #1.0 and 2.0)

The baseline forms and worksheets consist of the following:

Baseline Physician
Audiology Data
Audiology Eligibility
Contact Info
Self Report
Baseline Participant
Baseline Laboratory Measures
Retrocochlear Rule Out Form
Eligibility Checklist
Randomization
Oral Treatment or IT Treatment
Pain Scale
Adverse Events

10.3.1 Baseline Physician

The *Baseline Physician* form is completed by the Clinical Site PI at the time of initial participant evaluation. The form has sections detailing SSNHL diagnostic criteria, exclusion criteria, otologic history, general and otological physical examination, and focused neurological examination.

10.3.2 Audiology Data Form

This form should be completed by a site audiologist who is trained and supervised for SSNHL activities by the site's Lead Audiologist. Instructions for completing this form are found in Chapter 5. The CRC should review the form for completeness and accuracy once it has been completed. The form has sections to designate at which visit the data were obtained, the affected ear, the pure tone audiometry scores, word recognition scores, and any special comments by the site's Lead Audiologist. This form is completed at the initial screening visit and again during treatment and follow-up visits as designated on the *Visit Table*.

10.3.3 Audiology Eligibility

The *Audiology Eligibility* form is designed to help determine that the audiology study criteria are met. The worksheet uses key information from the *Audiometry Data* form completed at the initial screening visit. Eligibility criteria are described in detail in Chapter 1 and are also noted directly on the form. This form is completed by the site's audiologist, reviewed by the Lead Audiologist and given to the CRC for use in determining each participant's overall eligibility to enroll in the study.

10.3.4 Contact Information

The *Contact Information* form provides information to Clinical Site staff on how to contact the patient during the day and evening hours, the best time to call the participant, and if it is acceptable to call the participant at work. In addition, the form asks for a friend's or relative's phone number for emergency contact. This form should be placed in the participant's study chart for future reference if needed.

10.3.5 Self Report

The *Self Report* form is used to collect information regarding race, gender, and ethnicity of each potential participant. It is mandated by the NIH that the study attempt to collect this information. However, it is optional for potential participants to complete the form and they may opt not to do so.

10.3.6 Baseline Participant

The lengthy *Baseline Participant* form contains questions on medication use and allergies, a detailed review of systems, and some social/personal habits. These questions about the participant's status at the time of initial evaluation are very important. This information will be used to help describe, in general terms, the individuals who enroll in the study and will be used to describe the participants in study reports and publications. This will also provide the baseline for comparison to review of systems information gathered at subsequent treatment and follow-up visits that will enable the CRC and others to monitor participants for adverse events.

10.3.7 Baseline Lab Measures

The *Baseline Lab Measures* will serve to document baseline data, establish participant eligibility, and monitor their safety These laboratory assays were chosen to ensure participant safety prior to beginning the study drugs, therefore these laboratory assays must be drawn prior to the administration of a study drug. The actual values resulting from the assay are not of interest to the study because local variations in techniques would lower the value of pooled data. Because of this, the study requirements involve reviewing test results and recording results as normal or abnormal. If abnormalities are reported, the CRC will be responsible for noting this, reporting it to the Clinical Site PI, and documenting this on the form.

Only hematocrit, white blood count, serum glucose, and urinalysis are mandatory *Baseline Laboratory Measures*. Pregnancy test is recommended in all women of child-bearing age who consider themselves "at risk." All other measures are obtained at the discretion of the Clinical Site PI based upon the patient's medical status.

10.3.8 Retrocochlear Rule Out Form

The *Retrocochlear Rule Out* Form is required to document that retrocochlear causes of SSNHL have been ruled out. The preferred method for retrocochlear rule-out is by gadolinium-enhanced MRI scan. However, some participants may be allergic to the gadolinium contrast agent, may be too claustrophobic to undergo MRI scanning, or may have ferromagnetic implants or other medical contraindications to MRI scanning. In this case the Clinical Site PI may opt for CT scan or ABR testing as an alternative means of ruling out demyelinating disease, neoplasm, or stroke.

10.3.9 Eligibility Checklist

The *Eligibility Checklist* is completed by the CRC using information taken from the *Audiology Eligibility* form, the *Baseline Participant* questionnaire, *Baseline Physician* form, and *Baseline Lab Measures* form. There are sections on clinical/diagnostic criteria for SSNHL, audiometric inclusion criteria, and otologic and medical exclusion criteria. Data entry boxes are shaded such that entry of a value into a shaded box indicates an exclusion from the study. If all eligibility criteria are met, there is a section to indicate whether or not the potential participant is willing to participate. If so, there is a section to indicate that *Informed Consent* and *HIPAA*

documents have been completed. If the potential participant is eligible for the study but chooses not to participate, there is a section to indicate the reason.

10.3.10 Randomization

The questions on the *Randomization Form* 52 will be answered by the CRC. Complete a hard copy of *Randomization Form 52* and send it to the Data Management Center with the other case report forms, keeping a copy in the patient's file. The procedure for obtaining a randomization number is detailed in Chapter 7.

10.3.11 Oral Treatment

The *Oral Treatment* form is the form on which the CRC will make entries at each scheduled treatment visit. In addition to noting the visit number and date, there is a section to note the actual and the expected pill count. This enables tracking of treatment compliance, one of the secondary outcome measures of the study. This form also has a section to indicate *Drug Dose Change/Stop* information. The form is completed by the CRC with input from the clinic physician if there is any drug dose change or stop.

10.3.12 IT Treatment

The *IT Treatment* form is the form on which the CRC will make entries at each scheduled treatment visit. In addition to noting the visit number and date, there is a section to note the status of the eardrum/middle ear on the affected side, the drug lot number and dosage administered, and the administration date. Recording the administration date enables tracking of treatment compliance, one of the secondary outcome measures of the study. This form also has a section to indicate *Drug Dose Change/Stop* information. The form is completed by the CRC with input from the Clinical Site PI if there is any drug dose change or stop.

10.3.13 Pain Scale

The *Pain Scale* is a visual analog ranking of ear pain that is completed by each participant at baseline enrollment and again throughout treatment and follow-up according to the schedule indicated on the *Visit Table*. Ear pain is one of the secondary outcome measures of the treatments in this study.

10.4 TREATMENT AND FOLLOW-UP FORMS (Visits #3.0, 4.0, 5.0, 6.0, 7.0, 8.0)

Individuals who meet eligibility criteria and choose to enroll in the study will begin treatment as soon as possible, preferably the same day as their screening and baseline/enrollment visit. During their treatment and follow-up there are a number of forms that will be completed on a schedule detailed on the *Visit Table*. These forms include:

Audiology Data
Pain Scale
Oral Treatment or IT Treatment
Adverse Event
Weekly Laboratory

10.4.1 Audiology Data Form

This is the same form used during the initial screening visit and all other visits in which audiometry is performed. The schedule for use of this form is detailed on the *Visit Table*. Completion of the form is detailed in Chapter 5.

10.4.2 Pain Scale

The *Pain Scale* is the same form used during the Visit #2.0.

10.4.3 Oral Treatment

The *Oral Treatment* form is the same form used at Visit #2.0.

10.4.4 IT Treatment

The *IT Treatment* form is the same form used at Visit #2.0.

10.4.5 Adverse Event

The *Adverse Event* form is the same form used at Visit #2.0.

10.4.6 Weekly Laboratory Form

The *Weekly Laboratory Form* is completed by the CRC to document safety monitoring data collected at each scheduled treatment or follow-up visit as detailed in the *Visit Table*. Elevation of serum or urine sugar could indicate diabetes, a possible AE arising from use of the study drugs. Appearance of cells in the urinalysis could indicate urinary tract infection, another possible AE arising from use of the study drugs.

10.5 SPECIAL FORMS

There are several SSNHL forms that will be used for special circumstances. These include:

Protocol Exception
SAE
SAE Follow-up Form
Unscheduled Visit
Missed Visit
End of Follow-up
Shipping Log
Missed Form
Data Change

10.5.1 Protocol Exception

The *Protocol Exception* form will be used if any protocol exception is applied to a participant. Protocol exceptions must be requested by the Clinical Site PI and approved by the Study Chair, both of which are documented on this form. The nature of the exception is also documented. The original form will be express mailed to the Study Chair's office for signature. The Study Chair will express mail the form back to the site who will follow the protocol for mailing to the Data Management Center.

10.5.2 Serious Adverse Events

All SAEs occurring during the study will be recorded on the *Serious Adverse Event* form. This form should be completed and overnight express mailed to the Study Chair within 24 hours

of identification of any SAE. The form includes sections describing the SAE, the dates of onset and resolution, and an assessment of whether or not the SAE is study-related, sections for detailed descriptions of the circumstances of the SAE.

10.5.3 Serious Adverse Event Follow-up

Until the SAE is resolved, this form is completed serially on a schedule dictated by the DSMB until a final disposition of each SAE is achieved.

10.5.4 Unscheduled Visit

This form is completed by the CRC to document the reasons for any and all unscheduled visits by a study participant to the Clinical Site.

10.5.5 Missed Visit

This form is completed by the CRC to document the reasons for any and all missed visits by a study participant to the Clinical Site. Missed visits can be an indicator of treatment compliance, a secondary outcome measure of the study.

10.5.6 End of Follow-up

This form is completed by the CRC and documents the final disposition of every study participant, as mandated by the intention-to-treat methodology of the study. Final disposition may be completion of the study, but may also be death of the patient, lost to follow-up, or withdrawal of consent.

10.5.7 Shipping Log

This form is completed for each participant by the CRC as a shipping invoice to go with each batch of data forms mailed to the Data Management Center.

10.5.8 Missed Form

This form is completed by the CRC to document any forms not completed at a visit. The reason for the missed form is specified.

10.5.9 Data Change

This form is completed by the CRC to document any change in original data already transmitted to the Data Management Center and entered into the study database. It documents the specific data change, the date of the change, and offers a space to enter comments or details.

10.6 FORMS

Examples of each form are located on the CD in Adobe Acrobat (PDF) format. The files are named:

FORM (##)-[form-name].PDF

For example, the *Baseline Physician* form is named: “FORM (02)-BASELINE-PHYS.PDF”. These files may be printed separately to give high resolution copies of any form needed during the study.

CHAPTER 11
ADVERSE EVENT REPORTING GUIDELINES

11.1 OVERVIEW

11.1.1 Adverse Events

An adverse event (AE) may be any reaction or undesirable event that occurs in conjunction with the use of a drug, biologic product, diagnostic agent, medical device, experimental procedure, or even accepted medical treatment (if part of a research protocol), whether or not the event is considered related to the drug treatment or procedures. Such events may be psychological, emotional, social and/or physical and include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the experimental study regardless of causal relationship to the drugs and procedures under study. Reporting of adverse events begins as soon as a patient signs consent to participate in the trial.

11.1.2 Serious Adverse Events

Adverse events are further classified as serious adverse events (SAEs). To ensure patient safety each serious adverse event must be reported to the Chairman's office within 24 hours (or one working day) of learning of its occurrence. A serious adverse event is defined in general as an untoward (unfavorable) event which:

1. is fatal or life-threatening,
2. requires or prolongs hospitalization,
3. is significantly or permanently disabling or incapacitating,
4. constitutes a congenital anomaly or a birth defect,
5. may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations occurring under the following circumstances: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the criteria above); are part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition.

11.1.3 Reporting to Your IRB

Generally, IRBs require expedited reporting of SAEs. In addition to the reporting requirements to the Study Chairman described above, follow the reporting guidelines of your IRB.

11.1.4 Treatment-Related Adverse Events

Although adverse event reporting begins at the time the consent form is signed, special emphasis will be placed in this study on reporting treatment-related adverse events (side effects). For the purpose of the study, a treatment-related AE is defined as any health related untoward effect that occurs while the participant is taking a study drug. Before enrollment, participants in the SSNHL trial will be informed about the possible side effects from study drugs and the

medical significance of these potential effects. During the course of the study clinic staff members will monitor all participants for the presence of side effects or treatment-related AEs. This is done in order to ensure the safety of the participant, as well as to collect data on the frequency and types of problems that occur in the different study phases. Careful and complete reporting of treatment-related adverse experiences is essential. For the purpose of the study, treatment-related adverse events include any laboratory safety monitoring levels that are of sufficient severity to warrant temporary or permanent discontinuation of the study drug. As with general adverse events, each event is further defined as a treatment-related AE or SAE.

Treatment-related adverse events are defined as symptoms that may be unpleasant and bothersome to the participant, such as minor infections, hair loss, nausea or other side effects from the drug that do not require discontinuing the study drug. Treatment-related adverse events are not harmful to the participant and usually do not require medical attention or treatment. This kind of event will likely be recorded by the participant on the symptom check list.

Treatment-related serious adverse events are defined as effects of study medication that may be harmful to the participant and/or may be severe enough to warrant either temporary or permanent discontinuation of the study drug, either because they are intolerable or because they are judged to be potentially harmful to the participant. The decision to interrupt the study drug rests with the Clinical Site PI and depends on the total clinical assessment of the participant.

Management of both treatment-related AEs and SAEs is based on the philosophy of protecting the safety of the participant while at the same time making every effort to adhere to the study protocol and the prescribed medication regimen. Suggested approaches to some of the more frequent problems are specified. Other less common experiences are not described, reflecting the idea that each Clinical Site PI will need the flexibility to use his or her own judgment for handling a wide range of problems that may develop in a fashion that will maintain the participant's safety and the integrity of the trial.

11.2 GENERAL GUIDELINES FOR ASSESSMENT‘

A complete medical history will be taken before a participant begins taking the study drug. A brief physical exam will be performed at each clinic visit by the clinical physician. In addition to the standardized symptom check list, which will be completed by the CRC at each visit, participants should be asked to report any new AEs or symptoms. This information should be solicited using nonspecific questions such as, "How have you been feeling?", "Have you been experiencing any problems?" Care should be taken not to phrase the question in a leading manner such as, "Is the medicine making you vomit?" These problems should be evaluated based on the medical judgment of the clinic staff; however every effort should be made to prevent interruption of the study drug except for serious AEs.

11.3 ADVERSE EVENTS

11.3.1 Assessment

There are several minor side effects that have been reported by individuals taking prednisone or methylprednisolone. Minor physical symptoms in each class are listed below. These side effects usually do not require medical attention.

1) Headache

2) Indigestion or nausea
3) Mood change, including nervousness, anxiety, or depression
4) Restlessness
5) Trouble sleeping
6) Increase in appetite
7) Weight gain or loss
8) Increased sweating
9) Increase in hair growth
10) Loss of hair
11) Mild infections
12) Mouth sores (small)
13) Amenorrhea
14) Acne

11.3.2 Management

Minor adverse symptoms may improve spontaneously during treatment; participant education, reassurance and encouragement by clinic staff will help compliance during the beginning of treatment. If symptoms continue or are bothersome, the response to or treatment of minor AEs is a matter for the judgment of the Clinical Site PI. If the physician chooses, he or she may recommend or prescribe treatment for the relief of minor symptoms. The following are some suggestions for management of some of the more common minor symptoms.

Headaches: acetaminophen

Indigestion or nausea: recommend taking the study drug in the evening, eating a small amount of food with the drug, and taking GI protecting drugs.

Irritability, anxiety, depression: determine if the sleeping pattern is normal for the participant, recommend reduction in caffeine consumption, recommend mild exercise such as walking etc., or anxiety therapy. The study physician may choose to prescribe lithium 300 mg/per day for symptoms of agitation and anxiety caused by prednisone.

Sleep disturbance: restrict caffeine consumption, recommend a relaxing activity prior to retiring for the night, avoid heavy meals in the late evening, and recommend an exercise program.

11.4 SERIOUS ADVERSE EVENTS

11.4.1 Assessment

Serious adverse events may be harmful to the participant, and may therefore require either temporary or permanent discontinuation of the study drugs. The Clinical Site PI or clinic staff may determine if the participant has been experiencing such an event through a participant initiated contact between scheduled visits, the interval history form or follow-up examination, direct contact from the participant's personal physician or family member, or a safety monitoring laboratory report.

11.4.2 Types of Serious Adverse Events

Serious adverse events are classified into the following categories and may or may not require interruption or discontinuation of the study drug:

1) Death
2) A life-threatening event (places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred)
3) In-patient hospitalization or prolongation of existing hospitalization
4) Persistent of significant disability or incapacity
5) Congenital anomaly/birth defect
6) Any other condition that, based upon medical judgment, may jeopardize the participant and require medical or surgical treatment to prevent one of the above outcomes

Examples of SAEs include: septicemia, hemorrhagic cystitis, leukemia or other hematologic malignancies, opportunistic infections (e.g. PCP, herpes zoster, meningitis), suicide ideation, uncontrollable high blood pressure, uncontrollable diabetes, acute liver injury, pancytopenia, avascular necrosis, compression fracture, and critical laboratory values.

11.4.3 Major Symptoms Associated with Study Drugs

1) Irregular heartbeats
2) Shortness of breath
3) Edema
4) Hypertension
5) Bloody or black tarry stools
6) Stomach pain or burning
7) Frequent urination‘'
8) Confusion
9) Excitement
10) False sense of well being
11) Mental depression
12) Hallucinations
13) Paranoia
14) Back or rib pain
15) Shoulder, knee or hip pain
16) Stress fractures
17) Rapid weight gain
18) Increased thirst
19) Infection
20) Decreased or blurred vision
21) Cataracts
22) Reddish purple lines on skin
23) Unusual tiredness
24) Pain or weakness

11.4.4 Laboratory Alert Values‘

Local safety monitoring tests will be conducted at baseline/enrollment and at

treatment and follow-up (Visits #2.0, 4.0, 6.0, 7.0, 8.0) to ensure participant safety. Results of these tests, and others ordered at the discretion of the Clinical Site PI, will be monitored by the staff at each Clinical Site. Any abnormalities judged by the Clinical Site PI to warrant changes in study medication dosage will be reported to the study Chair. If a dosage change or stop is in order, the CRC would indicate this in the *SSNHL IT or Oral Treatment* form *(*Form 10 or 11*)*. Those participants whose medication has been interrupted based on an AE or adverse laboratory value will have two weeks in which to resolve this problem. If after that time the laboratory value is still abnormal, the clinical event persists, or it is considered unsafe by the Clinical Site PI to resume therapy, the participant will be permanently withdrawn from the study medication and the *SSNHL IT Treatment or Oral Treatment* form is completed. These participants will continue to be followed according to the planned data collection visit schedule.

Aside from the required urinalysis, serum glucose, HCT, and WBC measures, any other safety or monitoring laboratory measures are obtained at the discretion of individual Clinical Site PIs as indicated by the participant's medical status. All tests ordered will be reported to the Data Management Center on the *SSNHL Baseline Laboratory Measures* form and/or the *Weekly Laboratory* form. If any results exceed normal limits for the Clinical Site's local clinical laboratory, repeat laboratory assessment will be obtained for the abnormality in question at the discretion of the Clinical Site PI.

11.4.5 Management

The *SSNHL Adverse Events* form is completed at every treatment and follow-up visit (all Visits #2.0 through 8.0). Some events will have resolved by the time they are identified at the Clinical Site during routine visits. In this case, an *SSNHL Adverse Events* form should be completed and a decision about continuation of study drug made. Other problems may be reported by the participant between clinic visits, at a normally scheduled follow-up visit, or come to the attention of the Clinical Site PI through the safety monitoring laboratory reports. In these situations, an *SSNHL Adverse Events* form should be filled out and a decision made for further diagnostic testing and/or treatment and the interruption or discontinuation of the study drug. Any interruption or discontinuation of the study drug requires completion of an *SSNHL IT Treatment or Oral Treatment form* (Chapter 10).

For temporary discontinuation due to side effects, participants will be allowed to return to study medications no later than two weeks after temporary discontinuation. Depending on the individual situation and discussions with the Study Chair, participants may either resume at the full or a lower dose.

Drug Toxicity Management

Toxicity	**Management**
Weight change	Counseling
CNS change (*e.g.* sleep change)	Counseling; control with medications
Mood change	Counseling; control with medications

Psychosis	Temporary discontinuation
Myopathy	Temporary discontinuation
Hypertension	Control with anti-hypertensive medication
Diabetes	Control with medication
Avascular necrosis	Termination
Pain during administration	Premedicate with analgesic
Otorrhea/acute otitis media	Temporary discontinuation; Treat with oral and/or topical antibiotics

11.5 REPORTING SERIOUS ADVERSE EVENTS

All SAEs require prompt notification to the Study Chair within 72 hours of the Clinical Site PI being made aware of the event. Prompt notification of an SAE should be made by sending the original SAE form (51) via express mail with narrative and supporting documentation to the Study Chair's via the Study Clinical Research Coordinator. The Study Chair will review the SAE and forward a copy to the Data Management Center and a copy to the reporting site.

The Study Chair will be responsible for evaluating all SAEs for participant safety concerns. All SAEs, both those that are related to the investigative treatment and those that are unexpected, will be reported to all Clinical Site PIs, the Data Management Center PI, the NIDCD Project Scientist, and the Chair of the DSMB. The Study Chair will be responsible for filing a report with the FDA when required (see Section 11.5.1)

The Study Chair working with the Data Management Center will generate tabulations of AEs and present a summary of all AEs and SAEs to the DSMB on a schedule set by the Board.

11.5.1 FDA Reporting Requirements

Under stipulations of the FDA IND approval granted to the SSNHL study, the Study Chair must report:

1) Any unexpected fatal or life threatening AE associated with the use of the study drug (intratympanic methylprednisolone sodium succinate) by telephone or fax no later than seven calendar days after initial receipt of information about the event
2) Any AE associated with use of the study drug that is both serious and unexpected in writing no later that 15 calendar days after initial receipt of information about the event
3) An annual progress report of the study within 60 days of the anniversary date that the IND went into effect

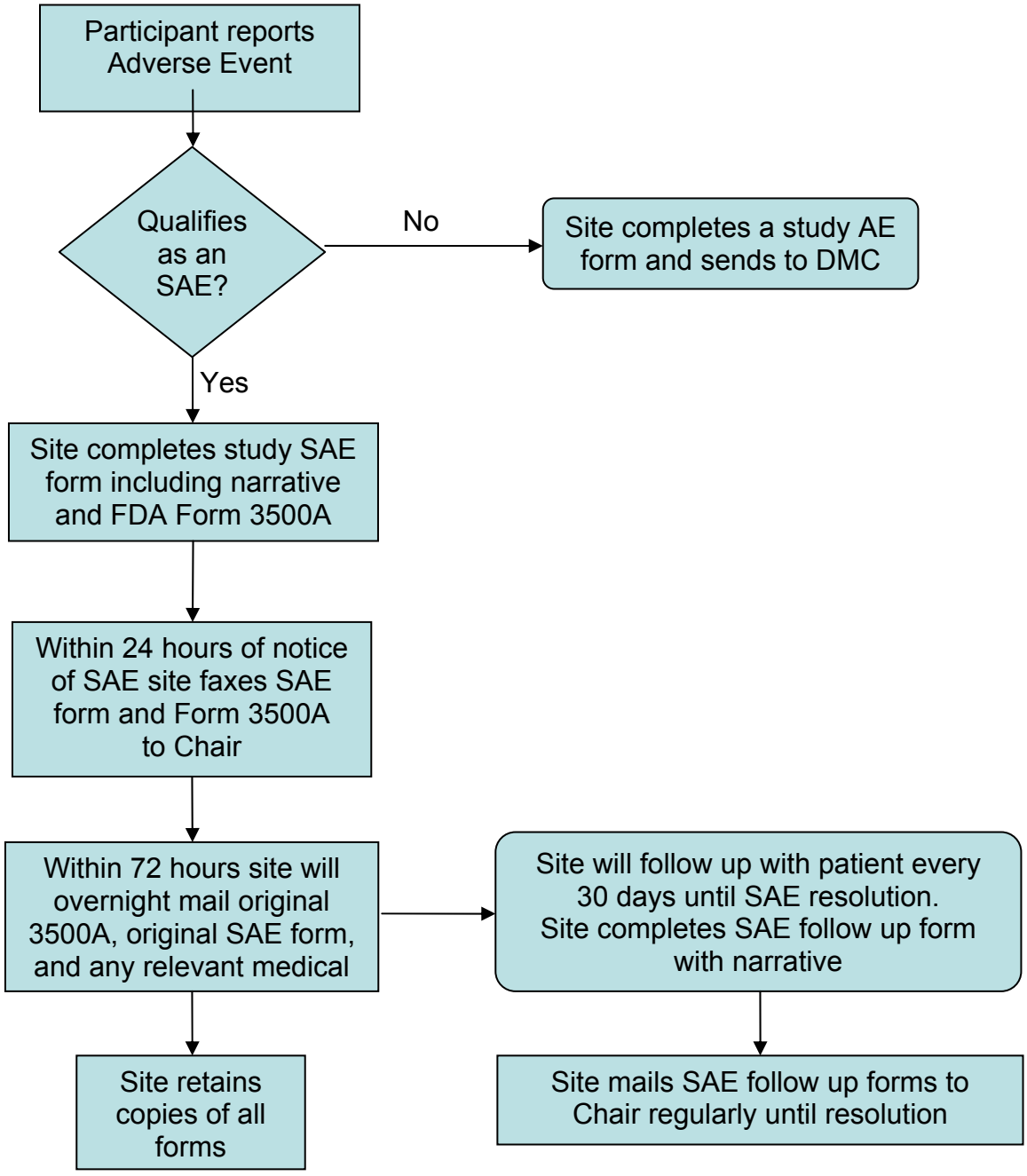
All information must be submitted on the FDA Mandatory Reporting Form 3500A (http://www.fda.gov/medwatch/REPORT/CONSUMER/INSTRUCT.HTM) or in narrative form in triplicate (identified by IND number) to the following address:

via Courier/Overnight Mail:

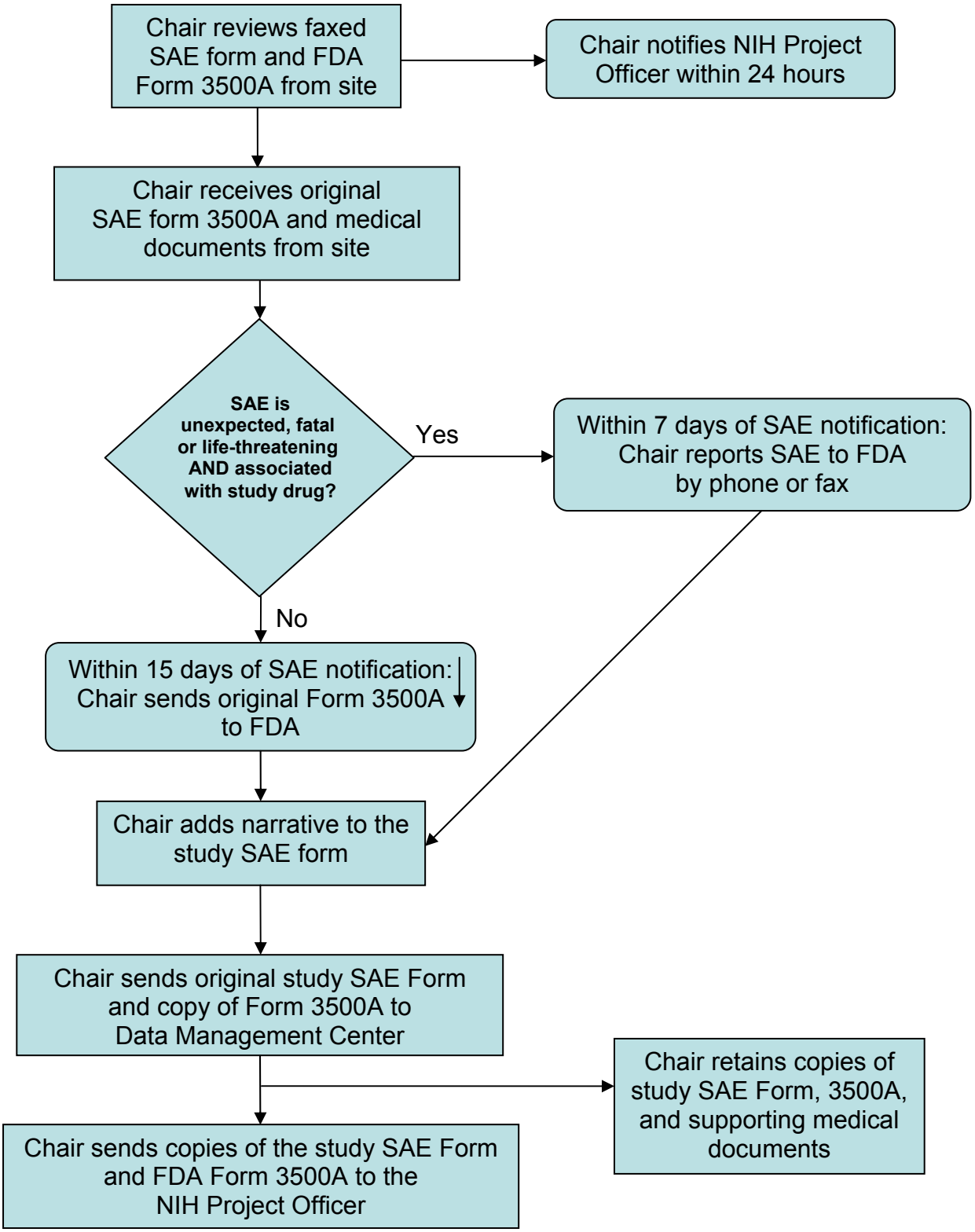
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Products, HFD-550
5901 B. Ammendale Rd.
Beltsville, MD 20705-1266

11.5.2 SAE Reporting Flow Chart

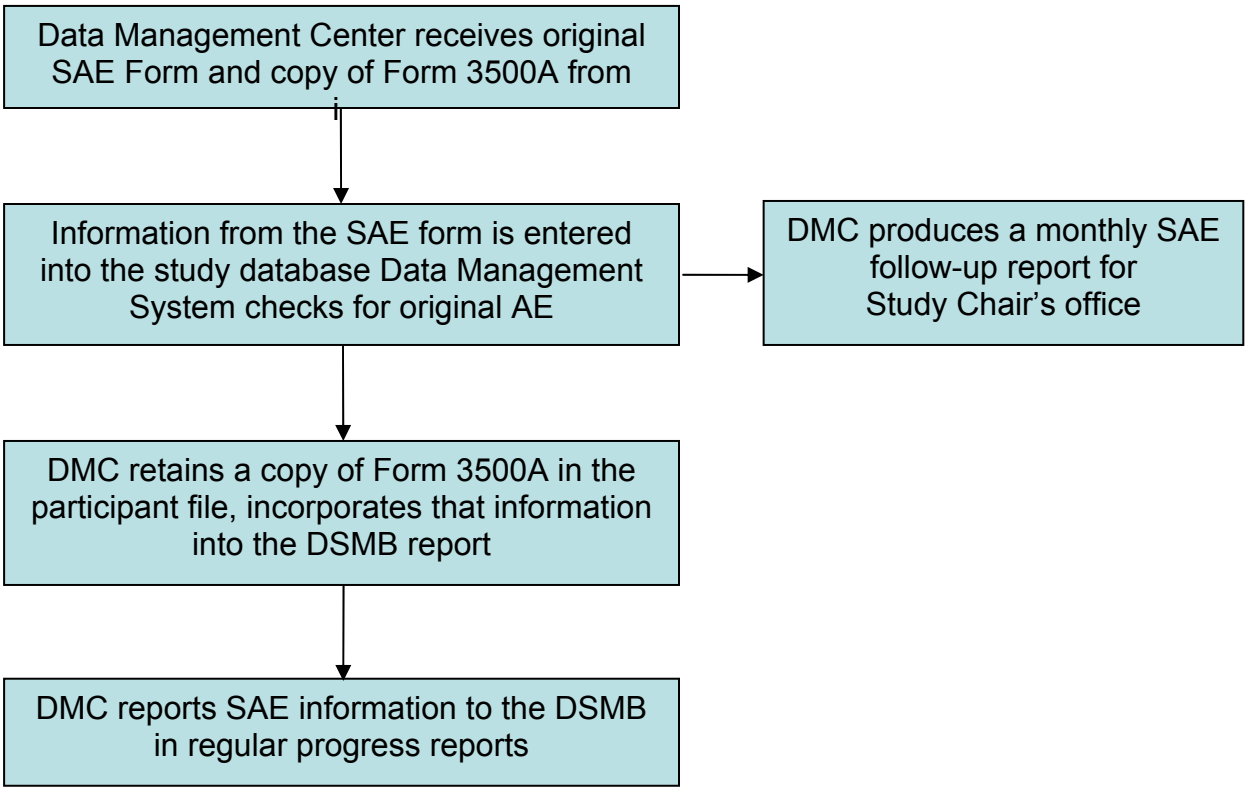
11.5.2.1 Initiation and follow-up at site:



11.5.2.2 Chair's Office SAE Report:



11.5.2.3 Data Management Center SAE Report:



CHAPTER 12
PROMOTION OF COMPLIANCE

12.1 INTRODUCTION

In the SSNHL study, all randomized participants, regardless of how regularly they attend clinic visits or adhere to and follow the protocol, will continue to be followed until the end of the study. The well-established "intention-to-treat" principle of clinical trial analysis will be followed: No participant will be dropped from the main analyses because of poor adherence. Therefore, it is critical that each participant is encouraged to maintain a high level of adherence/compliance with the study protocol after randomization.

Some general guidelines and suggestions that should be considered to help promote and improve adherence are presented in this chapter. These are techniques that have been employed in many other NIH trials. Not every clinic will be able to use every technique, but this discussion should be useful to clinics for planning their strategies to enhance compliance in the study.

Although the experience of other trials is useful, actual experience with participants will be invaluable in deciding what works and what does not. During the trial, clinics with good compliance records will be asked to share whatever compliance techniques they have found fruitful.

12.2 GENERAL DISCUSSION

Efforts to promote adherence should begin during the first clinic session, which will be the first time a potential participant will discuss the study with Clinical Site staff. At this visit, potential participants will be educated about some of the health concerns related to SSNHL. An informed person is more likely to comprehend the goal of the study: to help clinicians and patients make decisions about the treatment of SSNHL.

Although convincing evidence is lacking, it seems reasonable that a truly informed participant is also likely to adhere better. Therefore, for scientific, as well as ethical concerns, each potential participant should clearly understand the study and adequate time should be spent so that they understand what is expected of them. This should include a discussion of the main features of the study, the possible medication regimen to be followed over the duration of the study, laboratory tests and procedures required, and the timetable for clinic visits. A potential participant should be encouraged to consult with their family or private physician prior to signing the consent forms in order to minimize the chance that they may change their mind later and drop out.

From the beginning, the Clinical Site's staff should make it clear to the person what tests they will receive and when these tests will be performed during the course of the study.

Before enrollment, several steps will be taken to minimize compliance problems. First, because the study requires a dedicated commitment to taking intervention drugs, we must select appropriate participants and assess their potential for following the protocol before randomizing them.

Only those persons who are likely to follow the study protocol should be enrolled. Numerous studies have been conducted in an effort to determine what factors distinguish good and poor adherence. Factors related to socio-demographic status, disease therapy, and

investigators are among the many variables that have been studied. Only a limited number of variables have generally been identified as important.

One variable is the participant's belief in their susceptibility to the consequences of the condition or disease being studied, as well as their general feelings of vulnerability. Related to feelings of susceptibility and vulnerability is the participant's perception of the possible repercussions of an illness. If the consequences are believed to be serious, adherence to therapy (e.g. interventions) is usually high. An additional factor is how the participant views probable benefit from the intervention. Higher levels of education have been reported to correlate with good compliance. The overall quality of the environment at sites in multicenter trials have also been noted to influence adherence.

It is usually advisable to exclude certain types of people from participation in a trial. These would include persons addicted to drugs or alcohol, persons who live too far away, or those who are likely to move before the scheduled termination of the trial. In SSNHL, the judgment of Clinical Site's staff is essential in determining overall eligibility with respect to adherence.

It is especially critical in studies of long duration to maintain good compliance after randomization. Providing clear, easy-to-follow, written instructions for adhering to interventions, reporting side effects, returning for follow-up visits, etc. is a prerequisite. Reviewing these instructions with the participant periodically during follow-up should be a priority, especially if demonstrated compliance problems exist.

Staff should maintain close contact with randomized participants to get them involved and to keep them interested when their initial enthusiasm may have worn off. Means of involving the participant’s spouse or other family members in the study should be explored. Informed family members can be effective supporters of the study, often making sure that appointments are kept and adherence to the drug treatment is maintained.

Attempts should be made to maintain continuity of follow-up care. Whenever possible, the same Clinical Site PI, CRC, and Lead Audiologist should see the participant throughout the study.

Every attempt should be made to make each clinic visit pleasant. Minimizing waiting time and providing such things as parking facilities, free transportation, and comfortable waiting room facilities will make the visit more pleasant and make the participant more likely to keep their subsequent appointments. For a more detailed discussion, see Section 12.6, Promotion and Maintenance of Adherence.

12.3 MONITORING INTERVENTION ADHERENCE

Adherence to the intervention protocol is systematically monitored:

1) By tracking attendance at the clinic visits,
2) By pill counts of study drug and,
3) By self report from participant

The results of these measurements will be reviewed by the DSMB, the Study Chair’s Office, the Data Management Center, and the Steering Committee.

12.3.1 Pill Count

Pill count information will be collected at each treatment visit for participants randomized to receive oral prednisone. Additional pill count recalls may be suggested by the CRC to evaluate and promote adherence.

12.4 PROMOTING ATTENDANCE FOR SCHEDULED CLINIC VISITS

During the follow-up phase, participants are required to attend the clinic at regular intervals. Attendance at scheduled clinic visits is documented by the completion of the appropriate treatment and follow-up visit forms.

Clinics are advised to keep detailed records of rescheduled and broken appointments for each individual participant. It is important to monitor each participant and identify persons who need support.

12.5 MANAGEMENT OF NON-ADHERENCE

Plans should be made to handle problems such as non-adherence to drug interventions and chronic or occasional nonattendance at the clinic. The procedures discussed below may be used for handling and documenting these cases.

12.5.1 Missed Visits

Participants not attending the clinic visit during the required time frame are considered to have missed a visit. Careful documentation and monitoring of missed visits is important in the specific, as well as the overall, management of these cases. The following procedures should be implemented as appropriate in each Clinical Site:

1) Preparing for the next visit at the end of each current visit by making the appointment and giving instructions for the next visit
2) Sending out pre-visit reminders
3) Maintaining telephone contact with participants between visits
4) Establishing a mechanism by which clinic attendance for each participant can be charted and monitored locally so that the clinic can be immediately alerted to a missed visit
5) Immediately contacting (usually by telephone) the participant when they miss a visit
6) Planning clinic action to rectify the problem within the scope of clinic services
7) Rescheduling the visit, if at all possible, within the same window. (If an examination cannot be scheduled due to a participant's refusal, every effort should be made to obtain a telephone interview. Otherwise, an appointment should be scheduled to occur as soon as possible.)

12.5.2 Refusals

Some participants randomized into the study may not be actively participating, i.e. not adhering to the drug intervention and/or not attending the clinic. This may be due to any of a number of reasons, such as transportation problems, the advice from their private physician, or the participant's decision. Regardless of the reason, these participants should be followed until the end of the study and the clinic staff must attempt to make contact every six weeks. It may be possible to complete an interview over the telephone for the

purpose of checking participant status. These contacts are intended to remind the participant that they are still eligible to participate in the study even though they are off study drug. Considerable effort should be expended to collect audiology measurements and medication status at scheduled times.

12.6 PROMOTION AND MAINTENANCE OF ADHERENCE

The following guidelines may help to attain better adherence to the protocol, both in the area of drug intervention adherence and in clinic attendance. Resources available to a clinic will determine which techniques are most appropriate for that clinic.

12.6.1 Participant-Staff Relationship

The key element in successfully maintaining a participant in long-term treatment is the development of a personal relationship between the participant and individual members of the staff. Impersonal form letters or phone calls from someone not known to the participant are far less likely than personal contact to succeed in keeping a participant interested in the trial. This personal element in participant contacts cannot be overemphasized. The CRCs should get to know the participant and perhaps call between study visits. This is especially true if clinic staff are aware of problems the participant may be having.

12.6.2 Continuity of Care

In general, participants' appointments should be scheduled so that they can be seen by the same clinic staff members on each visit.

12.6.3 Clinic Environment

The clinic environment should be warm and pleasant and oriented to the comfort of the participant. Personal notes can be made of events in the life of the participant – these can be commented on at the next visit (for example, the birth of a grandchild). If possible and if resources are available, lunch might be provided or birthday cards sent. For other NIH studies, holiday get-togethers have provided an opportunity for the participants and clinic staff to get to know each other on a more personal basis.

12.6.4 Participant-Staff Communications

Good communication is essential. The consistency of care described in Section 12.6.2 will ensure consistent communication of instructions. Participants should also have a good working relationship with their physicians. In addition to consistency among staff in what is communicated to the participant, instructions should be clear and interactions should be friendly and individualized. The participant should be helped to understand the beneficial nature of their participation in this program, as well as any possible side effects from the drug interventions.

12.6.5 Convenience and Accessibility of Care

Examples of factors in the accessibility of care include clinic location, availability of transportation, and convenient clinic hours. Each Clinical Site is responsible for making visits easy for the participants, a factor critical to the ultimate success of the study. Depending on local circumstances, different approaches may be used, but no participant should be unable to attend the clinic because of transportation, hours of clinic operation, or

any similar circumstance. If necessary (and if funds are available), participants could be reimbursed for transportation. Pre-arranged parking should be available if at all possible. Appointments should be scheduled at times and on days that do not interfere with a participant's working schedule.

12.6.6 Time in Clinic

One element that may be of vital importance in keeping participants returning for clinic visits over a prolonged period is the time that it takes to be seen at each clinic. Total clinic visit time for a participant at any single visit should be kept to a minimum consistent with maintaining quality. If waiting is necessary, explain the situation and, if possible, offer the option of rescheduling. On the other hand, participants ought not to feel rushed or be made to feel unwelcome. Participants should feel that in any department they are as important as any other patients. Taking time to visit with the participants and having coffee and the daily newspaper available will help to establish this feeling.

12.6.7 Appointment Reminders

Like the rest of us, participants can forget appointments. Therefore, appointment reminders should be used to prompt participants to come for clinic visits and bring their pill bottles with them. A phone call from the CRC is more personal than a letter and a hand written reminder better than a typed note.

12.6.8 Interim Contact Between Scheduled Follow-Up Visits

During the screening and randomization phases and during the initiation of drug interventions and when the clinic process is still relatively new, clinic staff should contact participants by telephone to remind them of clinic appointments and check to see if they have questions or concerns.

During the follow-up period, interim telephone contact is also encouraged. A telephone contact will demonstrate a caring attitude by the clinic staff as well as provide some "long distance" supervision.

During the period between the follow-up visits, a participant may have second thoughts, have side effects, or develop apathy toward the study. These visits demand that the participant interrupt their normal routine and make a trip to the clinic. Participants with otherwise good intentions may find this an unwelcome task. It is especially important, then, that clinic staff maintain contact with participants between visits.

Early in the trial, adjustments to the intervention routine may be difficult. It might be useful to call participants after one week to ask how they are adjusting to the intervention.

The participant should not feel, however, that they are being "checked on." Early in the screening process, clinic staff might ask the participant if they would object to a telephone call before the next visit and ask what time of the day and which day of the week that they prefer to be called. The CRCs should determine the best time for calling the participant and schedule the calls accordingly, rather than leaving a message simply asking a participant to call back. However, the participant should be encouraged to call if they have any questions or problems.

12.6.9 Participant Identity with the Study

The clinics should focus on promoting participant identity with the study. Regular communication will encourage such identity. This could include the following:

1) Newsletters sent to the participants in the trial sharing information of interest. Information on the progress of the study could be included as an incentive.
2) Holiday cards
3) Notices of special events
4) Group events, such as educational programs
5) A letter from a significant person outside the study (e.g. NIDCD Project Scientist, the President of the American Academy of Otolaryngology, the director of the NIDCD) pointing out the importance of the study and the need for full cooperation on the part of each participant.

12.6.10 Involvement of Family Members

Family members' involvement should be encouraged. A pamphlet describing the trial for the family members may foster successful involvement. The spouse should be informed about the study's purpose, its general design and the study medication. The importance and need for full cooperation from each study participant should be stressed. The spouse or other household member could, for example, be invited to attend the clinic visits, especially the initial visits, or any group meetings that are held during the course of the study. Compliance with the study protocol is more likely to be good if the family members get involved in the process. They can also notify the clinic if something happens to the participant.

12.6.11 Staff Meetings

Regular staff meetings should be held to keep the clinic staff informed regarding individual and overall adherence problems and to plan strategies for improvement. An adherence chart should be developed and reviewed for each participant and kept with the participant's record. Notes or clinic visit summaries can be used to indicate adherence problems. The Clinical Site PI should be readily available and willing to take personal action or give assistance when adherence problems make their involvement advisable.

12.6.12 Relationship with Private Source of Care

Good communications and maintenance of a positive relationship with the participant's private physician or other outside source of care are important. The physician should be kept advised of the participant's clinical course by reports of abnormal laboratory findings, physical examination findings, and other pertinent information, including any clinical problems encountered. A good rapport with the private physician and his or her support and cooperation with the protocol is essential to a high degree of compliance.

12.6.13 Re-education

If necessary, a review at each visit of the program with the participant, especially those who are poor compliers, for the purpose of promoting compliance can be a strong motivation. At this review, the CRC should discuss with the participant the purpose of the study, general features of the study, and what the length of the planned follow-up is (this is

easily forgotten). In addition they should review the written instructions given to the participant at the beginning of the study.

CHAPTER 13

DATA MANAGEMENT

13.1 OVERVIEW

The goal of data management activities in the SSNHL trial is to provide a high quality database reflecting the audiologic status of participants, ensuring the safety of participants, and allowing the best opportunity to assess clinical differences between treatment groups. In order to accomplish this goal, a system with checks to minimize missing data and to ensure the validity of the data will be developed. Data management is a cooperative effort of the Study Chair's office, the Clinical Sites, and the Data Management Center. Success is dependent on the coordinated efforts of all these groups. A secondary goal of the data management system is to facilitate communications to ensure accuracy and reliability of the data.

13.2 GENERAL DATA COLLECTION ISSUES

13.2.1 Study Office Requirements

The CRC and Lead Audiologist should have office space that is easily accessible to the Clinical Site PI and study participants. The office should be equipped with a desk, telephone, locked file/storage space, and a consultation/examination area that ensures the privacy of the participant. File cabinet(s) must accommodate individual file folders for each study participant, as well as study-related correspondence. There should be adequate space for storage of study-related materials such as forms, protocols, manuals, mailing containers, log books, etc. Necessary office/laboratory equipment should be located in a well-lighted, clean, and pleasant area and always maintained in an orderly fashion. Access to a fax machine and copier will also be needed.

All study personnel offices should be stocked with common office supplies such as pens, pencils, stapler, paper, tape, calendar, mailing envelopes, etc.

13.2.2 Required Supplies for Creating a Participant Filing System

1) Filing Cabinet: At most one standard metal filing cabinet will be needed to hold all the study-related files and supplies of blank case report forms per hospital.
2) File Folders: Letter-size manila file folders are probably the easiest to use. An ample supply of folders should be obtained and kept accessible.
3) Filing System: A separate file folder should be maintained for each participant who signs the consent form. All the study files for these participants should be stored in a locked file cabinet and filed sequentially by the assigned participant number.

13.2.3 Starting a Participant's File

1) Labeling the file folder: The participant's participant number should be legibly written on the individual file folder tab along with the participant's ID number. When contacting the Study Chair's office or the Data Management Center about any study participant, refer to the participant's ID number.
2) Materials to be stored within the file folder: The following materials should be stored within a participant's file folder: a copy of the signed consent form, and copies of all the study forms. Any other participant records necessary to track participant's progress through the study should also be stored in the file folders.

3) Order of stored materials: The materials should be stored in the following order with the consent form appearing first in the file, followed by all study forms filed sequentially by visit and form number. Other participant records should follow.

13.3 GENERAL CODING INSTRUCTIONS FOR PAPER FORMS

The objectives of the protocol can only be achieved through careful collection and recording of the data throughout the course of the study. The data collection forms have been specifically designed to capture the data and sequence of events of each participant screened or enrolled in the study. Clear, concise and complete data recording is essential and is the responsibility of all study personnel.

A fine point blue ink pen should be used to record data on the paper forms in order to maximize the readability of the forms. Write neatly on the forms. The single largest source of error in data management is the misinterpretation of the work of other study staff. Be aware that 1's, 2's and 7's are the most likely to be confused. Develop habits of making a clear right stroke at the bottom of a 2 (that distinguishes it from a 7) and not using the downward stroke at the top of a 1 (that can make it look like a 7). If you make mistakes mark through it with a single line, record and circle the correct response, and initial it. Review forms after you have completed them looking for places where your responses may not be clear. This will make it easier for the entry staff at the Data Management Center to keypunch the data into the database.

Each participant form contains unique identifiers. These identifiers consist of site number, the participant number, the participant's initials, the visit number, and the date of the visit. These should be entered in the designated place at the top of each form. If a form spans multiple pages, then these identifiers should be entered at the top of each page to avoid confusion should the pages become separated.

13.4 CASE REPORT FORM IDENTIFIERS

13.4.1 Site Codes

Each of the sites is assigned a three-digit hospital code which will be used as the first three digits of the participant's unique identification number.

13.4.2 Participant's ID Number

After a participant signs the consent form and is entered into the study, a three-digit number is assigned to him/her for identification purposes. These numbers are assigned sequentially by the site starting with 001. This number combined with the site code forms a unique identification number for a particular participant. For example, if John Jones was the first person entered at Clinical Site 200, then Mr. Jones' identification number would be assigned as 200 001. All study forms must contain this number.

13.4.3 Visit Number

Scheduled visits are numbered as 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 (see Visit Table, Chapter 10). Any interim unscheduled visits will be numbered such that the digit before (to the left) of the decimal point denotes the last scheduled visit and the digit after (to the right) of the decimal point provides sequential numbering of unscheduled visits in this interim between scheduled visits. For example, if the last scheduled visit was 3.0 and the participant makes two unscheduled visits before their next scheduled visit (4.0), they

are numbered 3.1 and 3.2. Unscheduled visits between scheduled visits 4.0 and 5.0 would be numbered sequentially as 4.1, 4.2, etc.

13.4.4 Participant's Initials

If the participant does not have a middle initial, insert a dash in the middle space.

13.4.5 Date

Each form should include the date of the visit being reported. Whenever a date is entered on a form, the eight-digit code (mm/dd/yyyy) must be used: the first two digits for the month, the next two digits for the day, and the last four digits for the year. For example, March 12, 2002 should be coded as 03 12 2002.

13.5 DATA FIELDS

For multiple choice items, circle the appropriate box. Only one box per question may be circled unless otherwise indicated. For "fill-in-the-blank" items, enter the appropriate number or letter in each box. In numeric cases in which there are more boxes than necessary for the number of digits in your response, place all numbers as far to the right as possible (paying appropriate attention to any preprinted decimal points) and put in leading zeros to fill the remaining boxes. For example, 90 dB HL should be coded as "090" in its three-digit field. When decimal places are used, the decimal is preprinted on the form. Insertion of decimals other than those printed on the form is not allowed. Place zeros in boxes after decimal point if appropriate. DO NOT insert a dash, negative sign, slash mark, or any other mark to fill in blank boxes unless instructed to do so.

13.6 ROUNDING

If a value requires rounding, round upward for any digits greater than or equal to 5. Digits less than 5 should be rounded down.

13.7 MAILING OF PAPER FORMS

13.7.1 Review of Forms

All forms should be reviewed for completeness prior to mailing. The Clinical Site PI will sign the shipping log indicating that he/she has reviewed the data.

13.7.2 Making Copies

Make photocopies of each completed form. Retain the photocopy and send the original to the Data Coordinator at the Data Management Center. Do not send the consent form, but when the participant is randomized, fax Form 93, *Notice of Informed Consent*, to the Data Management Center.

13.7.3 Documenting Forms that are Mailed

In each package of mailed forms, a completed Shipping Log should be included. This form 1) identifies all forms that have been completed and mailed, and 2) provides reasons why a particular form was not included in the package. As each component of the examination is completed, 'yes' should be circled on the shipping log next to the appropriate form number. After an examination is complete, any required forms that were not completed should be identified and the reason why that form was not completed should be provided.

13.7.4 Preparing the Mailing Envelope

Use an envelope that can accommodate the forms without folding them. Write the package number on the mailing label. The CRC should record all envelopes mailed on the Mailing Log, listing the date of mailing, the package number, and the ID of the participants whose examinations are included in the mailing. The package number should be assigned sequentially beginning with "001". This will assist the Data Coordinator in determining whether a package has been lost in the mail. It is acceptable to mail forms for several participants in one large package, but each participant's forms must be in an individual envelope within the larger package.

13.7.5 Mailing

Completed case report forms including the examination log should be mailed biweekly to the Data Coordinator at the address listed in Appendix A. Please use Federal Express, Airborne, or some form of direct express mail to enable tracking. Either overnight or 2-3 day delivery is acceptable.

13.8 NARRATIVE DESCRIPTION OF DATA FLOW

1) Prepare for the visit by having an adequate supply of copies of the forms in an easily accessible location.
2) Complete all necessary forms at the visit and review them.
3) Complete the Shipping Log and include it with the forms
4) Make copies of all completed forms and place them in the participant's file. Mail all original forms along with the Shipping Log to Linda Graham, Data Coordinator at the Data Management Center.

13.9 DATA MANAGEMENT IN THE DATA MANAGEMENT CENTER

Once forms are received and checked by the Data Management Center personnel, they are then submitted to data entry, where they are assigned a batch number and entered into an electronic format. Once in an electronic format the forms are processed using an in-house developed Interactive Data Management System and stored in a master database. At the time of processing validity checks are performed on major identifiers. If any unlikely values are identified, then they are verified with the site's CRC and corrected before the batch is added to the master database.

Every month two reports identifying potential problems are generated from the master database and sent to the Clinical Sites for resolution. First, forms that are overdue are identified in the *Overdue Forms Report*. For each clinic who have overdue forms (based on the date of the Baseline Visit and then the expected date of subsequent visits), the Data Management Center will FedEx an *Overdue Forms Report* to the Clinical Site staff. Within a two-week period, the Clinical Site's staff will either send the overdue form(s) or if the form(s) is/are permanently missing they will complete Form 55: *Missing Form.* Forms not returned within a month will reappear on the *Overdue Forms Report* until resolution. Secondly, the *Data Error Report* lists missing, suspect, or impossible data values within the forms. Within this report, both newly/ identified errors as well as unresolved errors are noted. For each data item, the Clinical Site's staff is provided the old data value (as indicated on the form), and asked to either approve the data item or provide a new and valid value. If the data item is permanently missing the CRC will enter "PM" (permanently missing). Data items will remain on the error report until resolution.

Both reports should be returned to the Data Management Center with the biweekly shipment of data. The responses to these discrepancies will be incorporated in the subsequent weeks' reporting.

13.10 STANDARD CLINICAL SITE REPORTING

In addition to the reporting of potential discrepancies in the database, monthly recruitment reports and semi-annual progress reports are provided to the Clinical Sites to assess the progress of the centers and overall study.

CHAPTER 14

QUALITY CONTROL

14.1 CERTIFICATION

Study-wide quality control is the ultimate responsibility of the Study Chair's Office, the Clinical Sites, and the Data Management Center. The CRC at each Clinical Site must become familiar with the SSNHL study's requirements and schedule clinic activities so that there is adequate time for clinic staff to carry out their responsibilities while meeting quality standards.

Training or education is required for all of the study's personnel to have a clear understanding of the protocol and MOP and for standardization of procedures at all Clinical Sites. In this chapter, both general and specific procedures will be described.

14.1.1 Audiologic Evaluations

All Lead Audiologists must be trained by the Senior Study Audiologist prior to performing audiology measurements for the study (see also Chapter 5). Lead Audiologists will be responsible for the testing of all of the study's participants. They may train and supervise other audiologists involved with testing of participants. Lead Audiologists will review and complete the audiology forms and submit them to the CRC for review prior to shipment to the Data Management Center.

14.2 CONTINUOUS QUALITY CONTROL EFFORTS

14.2.1 Clinical Site Activities

Specific quality control activities to be carried out at the Clinical Site include:

1) Training of audiologists in specific measurement and data management by the centrally trained Lead Audiologist
2) Monitoring of regular equipment maintenance
3) Recording of participant identifiers on the top of each form prior to their completion at all clinic visits
4) Regular observation and monitoring of clinical procedures including specimen collection
5) Monitoring and editing of study data prior to mailing forms to the Data Management Center
6) Compilation and review of data on lost laboratory samples, packaging problems, errors in packing, shipping, and labeling of specimens
7) Reporting of quality control concerns or problems to the Study Chair's Office and Data Management Center for prompt resolution.

The CRC and/or Clinical Site PI should regularly monitor site procedures to be sure that they are being carried out properly and with consideration for the participant. Corrective action should be taken immediately if problems are observed.

The Clinical Site's staff are encouraged to communicate with the Study Chair's Office and Data Management Center about quality control or other concerns or problems.

14.2.2 Equipment

Each Clinical Site is responsible for the proper operation and maintenance of equipment used in the trial. All equipment used in the audiometric evaluation is already subject to standard calibrations and inspections. The Lead Audiologist is responsible for compliance with these standards. All staff should report any real or suspected equipment problems to that individual promptly.

All standard maintenance for the audiometric equipment and freezer (UCSD laboratory) should be documented and recorded by date in a permanent log and/or electronically. Problems and solutions should also be recorded. Copies of calibration records must be kept on file by the Lead Audiologist. The log and calibration records will be inspected during periodic site visits, or copies may be requested by the Study Chair's Office at periodic intervals. Please refer to Chapter 5 for a complete description of required equipment maintenance and calibration.

14.2.3 Data Quality

Each individual participating in the study will be assigned a participant identification number (as described in Chapter 12). Follow-up forms are further identified by the visit number indicating the interval at which the forms were completed (e.g. Visit #2.0, 3.0, etc.). The data entry system ensures that the participant's ID number is unique by permitting only one ID number to be entered for each questionnaire/form at each data collection point.

The CRCs are asked to review all of the participants' questionnaires, prior to ending each clinic visit. Forms must be completed neatly and accurately, and every question should be answered. Written responses to any items on the questionnaires/forms should be legible.

Review of the completed forms will be done again at the Data Management Center. The Project Manager will verify that the forms are legible, and that they have been filled out correctly and completely. Any problems identified will be resolved before the data entry step. If necessary, the Clinical Site will be contacted to provide missing information or to correct invalid responses on the forms.

The data entry screens will be designed to mirror the paper data collection forms to allow smooth flow from item to item and thereby minimize error with data entry. Verification of participant identifiers and visit numbers will be incorporated into the data entry system in addition to gross range checking of fields. The Data Management Center will routinely re-key a sub-sample of data forms to assess data entry accuracy and correct errors. Reports of error rates will be provided to the Steering Committee. The target error rates for SSNHL are $\geq$ 0.2% per field.

The Data Management Center will regularly perform internal comparisons of the entered data to detect missing records or suspicious or invalid data. These comparisons will include logical consistency checks of data within and across forms/questionnaires. Error reports will be generated and sent to the Study Chair's Office and Project Manager of the Data Management Center for resolution and for re-entry of corrected data. When inconsistencies are detected, the CRC will be notified through error reports, and will be asked to verify, if possible, some entries Prompt action with these verification requests is

essential for an efficient quality control system.

Quality control of study data will also be carried out locally on a continuous basis. Invalid and incomplete forms may be corrected prior to sending data to the Data Management Center. In addition, monitoring and/or error reports generated by the Data Management Center will be transmitted to the CRCs for review and action.

14.2.4 Laboratory Sample Collection and Processing

Blood and urine samples are required at certain scheduled visits, the majority of which will be tested in local facilities. Copies of local laboratory certification should be kept on file at the Clinical Site. In addition, blood samples for archival storage need to be collected, processed and shipped to the UCSD lab. The CRC will monitor the collecting, processing, and shipping of these serum samples.

14.2.5 Data Management Center

Quality assurance will be a major activity of the Data Management Center throughout the study. Activities will include:

1) Training/retraining of Clinical Site staff in data collection procedures
2) Rechecking all completed questionnaires/forms sent by the Clinical Sites prior to data entry
3) Data control (filing, manual editing, special coding efforts)
4) Monitoring of data entry activities and error rates
5) Documentation of database changes

Monitoring of the study data will take place at the Data Management Center. These activities include validation, data control, and report generation. Some of the monitoring and quality control reports will be transmitted to the Clinical Sites for immediate action and attention; other quality control and monitoring reports will be generated for the Study Chair's Office, Steering Committee, and DSMB. For example, these reports will include data on:

1) Recruitment yields at each Clinical Site
2) Summaries of certifications
3) Audiology measurement errors and other monitoring reports
4) Problems observed or reported at site visits
5) Adverse events
6) Deviations from protocol
7) Missed visits, refusals, losses to follow-up
8) Adherence
9) Errors in collection, labeling, storage, shipping of laboratory specimens

It is the responsibility of Data Management Center personnel to review these reports on a timely basis, to initiate action to remedy any problems as soon as possible, and, if necessary, to participate in site visits at the Clinical Sites, as well as to perform follow-up evaluations of actions taken.

14.2.6 Project Scientist and Steering Committee Reports

During the recruitment period of the trial, monthly reports on recruitment activities by each Clinical Site will be provided to the Study Chair's Office, the Steering Committee, the Clinical Site PIs, and the NIDCD Project Scientist.

During all phases, monitoring reports and analyses will be generated for each Clinical Site and the whole study. These will be reported to the Study Chair's Office and the Steering Committee.

Annual reports will include a summary of quality control data by Clinical Site.

14.2.7 Data Safety Monitoring Committee Activities

The DSMB is an independent panel of experts who review and advise on the scientific and operational progress of the study. The DSMB will periodically review and evaluate data on recruitment, quality control, compliance, AEs, and fatal and nonfatal events. This panel will report directly to the NIDCD and may recommend corrective action, changes in the protocol, or early stoppage of the study. The DSMB will also review and advise on proposed changes in the protocol originating from the Steering Committee and proposals for ancillary studies.

14.2.8 Changes in the Manual of Procedures

Changes in the MOP may need to be made from time to time. When this is required, a notification and the revised pages will be sent to all Clinical Sites. All obsolete pages/sections should be filed for reference--do not discard. IRB approval of any modifications of the protocol must be sought and obtained from each Clinical Site.

If a major procedural or design problem occurs, the Executive Committee will be asked to make a recommendation, the change will be made as above, and the Steering Committee will be asked to approve these changes at their regularly scheduled meeting.

14.3 SITE VISITS

During recruitment and follow-up, the Study Chair, Senior Study Audiologist, Senior CRC and personnel from the Data Management Center will visit each Clinical Site to promote communication, answer questions, and ensure that study procedures are understood and carried out correctly. The site visit program will provide a mechanism to encourage the effective and standardized delivery of recruitment efforts, intervention programs, and the collection of appropriate and valid data within each of the Clinical Sites. Site visits may also be performed if consistent departures from the MOP are detected. Retraining may be done as needed during these visits.

Before the visit, the Clinical Sites will be sent a proposed agenda and a schedule will be worked out in advance. The Clinical Site PI, CRC, and Lead Audiologist, as well as other staff members, will be involved. The first round of site visits should occur after experience has been gained with the first wave of participants. This will enable us to look at recruitment efforts, the methods of process and procedures, and any staffing problems clinics may be encountering.

The site visit will be an ideal time for suggesting solutions for any problems which are identified. Of equal importance will be the lessons that site visitors gain while watching other centers in action. The observational experience can enhance and increase the visitor's own skills

at developing problem solving strategies and solutions. Consequently, the site visits will be a time when the Study Chair's Office, Clinical Site, and Data Management Center staff review progress and problems, share what has/has not worked, and consider new strategies and solutions.

After each site visit, two types of site visit reports will be prepared. The first will be a frank discussion at the end of the visit between the site visit team, Clinical Site PI, CRC, and Lead Audiologist. The site visit team will prepare written reports on the findings of the site visit. A detailed report of the team's observations and recommendations that subsequently will be sent to the Clinical Site PI of the site being reviewed and the NIDCD Project Scientist.

14.3.1 Organization, Recruitment and Data Collection

The site visits are designed to insure that each Clinical Site is recruiting appropriate individuals and collecting high quality data. Objectives for the site visitor are a) to determine if the protocol and MOP are being followed, and if not, what measures should be taken to correct the problems and b) to learn as much as possible from Clinical Site staff about how to improve effectiveness in meeting recruitment goals, collecting data, and facilitating a smooth clinic flow.

A key to a successful site visit is adequate preparation both the Study Chair's Office, the Data Management Center, and the Clinical Sites. The visits should serve to enhance communication throughout the study.

Questions for the Clinical Staff: During the site visit, a visitor should seek answers to the following questions, review and discuss data reports provided by the Data Management Center, and explore any concerns or questions that arise.

1) Are clinics adequately and appropriately staffed to provide for effective recruitment, data collection, data entry, and intervention delivery? Do staffing patterns match those in original grant proposals?
2) Are staff roles clearly defined and is there communication and interaction between the various working groups?
3) How is information shared, for example, changes in the MOP?
4) What is the overall view of clinic flow?
5) The clinic tracking system will be discussed and the following questions may be asked.
   a) What is the procedure followed when a participant does not show up for his/her appointment?
   b) How does the clinic keep track of where an individual is in the study flow so that the participant is scheduled within the appropriate window?
   c) How are problem participants handled?

During the site visit, a visitor may ask to follow a participant through a visit, observe a randomly selected interview and observe audiology evaluations.

Chart Reviews:

1) Questions will be asked about where records are kept and how participant confidentiality is assured.
2) A site visitor will review selected charts to look at the following:
   a) Informed consent

b) Appropriate signatures
c) Complete data forms and cover sheets
d) Source documents

Manual of Procedures: The following questions concerning study documentation should be answered during the course of the site visit.

1. Where is the MOP located in the clinic and do clinic staff have easy access to it?
2. Does the MOP have all the updates included?
3. What is the procedure for maintenance on machines? Where are the quality control logs documenting that the audiometers are checked at appropriate intervals?
4. Where are laboratory certifications kept?
5. Where is the IRB approval document? Has the IRB been informed of protocol changes?

Preparation for the site visit by the center to be visited will be among the most valuable aspects. Preparation should include:

1) Distribution of the site visit guidelines
2) A review of compliance with the guidelines during staff meetings prior to site visits; and
3) A self-evaluation of clinic strengths and weaknesses in preparation for discussions with site visitors

Post Site Visit Activities at the Clinical Site should include:

1) A staff meeting to debrief the Clinical Site staff regarding information and issues related to the site visit;
2) Review of the written site visit report when available; and
3) Goal setting and planning based on site visit recommendations

Lab: The site visitors will observe how blood is handled and stored, and may ask questions about shipping and how OSHA regulations are being followed.

Data Quality Control Reports: The site visitors may review and discuss data reports provided by the Data Management Center, and explore any concerns or questions that arise. Possible items for discussion include: data edits, missing/delinquent forms, missed visits and protocol violations.

CHAPTER 15
SPECIAL TOPICS

15.1 INTRODUCTION

This chapter presents basic information on several topics related to study administration and organization.

15.2 CHANGES IN THE MANUAL OF PROCEDURES

The SSNHL MOP will be updated throughout the study to reflect suggestions, changes in the protocol or procedures, changes in the study organization or administration, and omissions in earlier versions. The Study Chair's Office and Data Management Center will keep copies of all sequential MOPs. The Clinical Sites are expected to keep copies of the current version of the MOP. Internal Review Board approval of any modifications of the protocol must be sought and obtained from each Clinical Site, and kept on file for each revision.

When changes are made to the MOP, the Study Chair's Office will circulate copies of all pages affected by the changes. The Clinical Sites will be required to insert these updated pages in their MOPs, and may discard earlier versions of these pages. Each page of the MOP will include a version date: only the most recent version should be included in the Clinical Site MOP. Site visits from the Study Chair's Office and Data Management Center representatives will include an inspection of the Clinical Site's MOPs to ensure that they are maintained and up-to-date.

15.3 DISTRIBUTION OF MEETING NOTES

Minutes should be circulated no later than one month after the date of the meeting. The Data Management Center will maintain a master archive of the minutes of all meetings. Production of minutes for formal meetings will be assigned, as follows:

	Minting Responsibilities	Minutes Distribution List
Steering Committee	Data Management Center	All Formal Steering Committee Members
Standing Committees	Committee Chair	Committee Members, Principal Investigators, Program Officers
Data and Safety Monitoring Board	Project Scientist	Committee Members and Appropriate NIH Staff

15.4 PUBLICATION POLICIES

The Steering Committee will develop a detailed publications policy. Copies will be distributed to all Clinical Site PIs and the NIDCD Project Scientist. As described in this document, the goals of this policy are:

1) To assure and expedite orderly and timely presentation to the scientific community of all pertinent data resulting from the SSNHL study;
2) To have accurate and scientifically sound presentations and papers.
3) To assure that all investigators, including those of junior faculty rank and other professionals have the opportunity to participate and be recognized in study-wide presentations and the preparation of SSNHL papers;
4) To assure that press releases, interviews, presentations, and publications are accurate and objective, and do not compromise the collaborative trial and the acceptance of its results; and
5) To establish procedures for review and approval of ancillary study applications.

15.5 STUDY ORGANIZATION

The organizational structure for the SSNHL project includes the following key components:

15.5.1 Study Chair and Study Chair's Office

The Study Chair and PI of the SSNHL project is Steven D. Rauch, M.D. The office of the Study Chair is located at the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. In addition to the Study Chair, the Senior Study Audiologist (Christopher F. Halpin, Ph.D.) and Senior CRC (Mary L. Bartley, R.N., B.A.) are at this site, which will also function as a Clinical Site. Each of these individuals will chair monthly conference calls with their counterparts at the other participating Clinical Sites to discuss, troubleshoot, and coordinate activities. These three individuals, along with the PI of the Data Management Center, will also comprise the group that makes quality assurance site visits to the other, participating Clinical Sites.

15.5.1.1 Study Chair's Responsibilities

1) Chairs the Study Group, which is comprised of all study participants
2) As an *ex-officio* member, along with the PI of the Data Management Center, keeps the DSMB informed of the progress of the study by providing annual progress reports. The progress report should be sent to all participants at least three weeks in advance of the annual meeting
3) Plans and attends, with the PI of the Data Management Center, all meetings of the Study Group and DSMB. Prepares minutes of all meetings of the Study Group. Minutes should be sent to the Data Management Center PI within three weeks after the meeting
4) Communicates with participating investigators; conducts site visits to participating Clinical Sites; and monitors quality control of the data
5) Works closely with the PI of the Data Management Center/Study Biostatistician in the statistical analysis of the data
6) Keeps all study personnel, including the Data Management Center personnel, abreast of recent presentations and publications related to the subject matter of the SSNHL study
7) Directs the development of presentations and publications of the study data

15.5.1.2 Senior Study Audiologist's Responsibilities

1) Serves as a contact among Clinical Sites, the Data Management Center, and the Study Chair regarding audiologic issues. Recognizes protocol and administrative complications in the study and brings them to the attention of the Study Chair
2) Maintains files of necessary documents, such as equipment calibration and the licensure and certification of the Lead Audiologists
3) Trains Lead Audiologists in data collection and correction procedures
4) Monitors and supports the performance of the audiologists as to protocol compliance, test materials, and standardization
5) Conducts monthly conference calls with Lead Audiologists; takes and distributes minutes
6) Participates in site visits
7) Works closely with the Study Biostatistician in the statistical analysis of the audiometric data.
8) Assists in the development of presentations and publications of the study data.

15.5.1.3 Senior Clinical Research Coordinator's Responsibilities

1) Assists in the development of forms and the MOP
2) Submits all documents needed to recruit participating sites. Obtains all documentation required for site participation.
3) Serves as a liaison between CRCs at the Clinical Sites and the Study Chair. Recognizes protocol and administrative complications in the study and brings them to the attention of the Study Chair and the Data Management Center.
4) Assure that approvals of the protocol, informed consent, and advertising are obtained from the sites' IRBs and reminds the sites about annual renewals of their IRB protocols
5) Makes sure that the Project Manager at the Data Management Center is copied on all regulatory documents including IRB approvals and renewed consent forms
6) Monitors the performance of the study participants as to protocol compliance, and participant accrual and follow-up.
7) Maintain files of SAEs on each participant entered into the study.
8) Conducts periodic conference calls with CRCs and Data Management Center personnel; takes and distributes minutes.
9) May coordinate the planning of dates, times, and locations of study meetings. Makes appointments and schedules; may coordinates arrangements for meetings, conferences and site visits.
10) Conducts telephone interviews of participants.

15.5.2 Clinical Sites

Each Clinical Site will be actively involved in the recruitment, evaluation and treatment of participants. Each site will consist of a PI (otolaryngologist), a CRC, a Lead Audiologist, and supporting staff who will provide the areas of expertise necessary for the successful completion of the protocol.

15.5.2.1 Clinical Site Principal Investigator's Responsibilities

1) Obtains approvals necessary to conduct the study at his/her site. These include obtaining local administrative and IRB approval, office and clinic space, and

support personnel.

2) Supervises the conduct of the study at his/her participating site to assure the successful conduct of the study and adherence to the protocol
3) Recruits participants into the study
4) Verifies that each participant is or is not eligible for entry into the study
5) Performs the informed consent procedure with all participants. All consent forms must be signed by the PI
6) Supervises the activities of the CRC and Lead Audiologist
7) Ensures that all paper report forms submitted to the Data Management Center are complete, accurate, signed, and sent twice a month
8) Responds to queries from the Chairman's Office or the Data Management Center
9) Attends study meetings
10) Retains all study-related documents as required by local IRB and compliance guidelines

15.5.2.2 Clinical Research Coordinator's Responsibilities

1) Checks clinic records frequently to identify possible candidates for the study. Establishes a routine system for the identification of potential participants.
2) Completes or assists in the completion of all case report forms for all study participants.
3) Checks all paper forms for completeness, accuracy and appropriate signatures. This includes correct coding for those data fields for which code lists have been provided. Ensures that packages of completed forms, along with specified supporting documentation, are sent in a timely manner to the Data Management Center.
4) Maintains a file for each study participant containing copies of all paper report forms and the original consent forms. Files should also include laboratory reports and other relevant test results. A progress note describing participant's progress since the last visit should also be included in the participant's file.
5) Obtains randomization assignment from the Data Management Center.
6) Ensures proper scheduling of follow-up contacts and the various tests and procedures necessary at visits.
7) Monitors participants for any study-related problems and reports these to the Clinical Site PI.
8) Responds in a timely fashion to questions from the Study Chair's Office or the Data Management Center concerning data.
9) Monitors the supply of study materials, especially study drug, blank forms. Informs the Data Management Center when the supply of forms is low.

15.5.2.3 Lead Audiologist's Responsibilities

1) Assures standard calibration and proper functioning of all audiology equipment and installations
2) Verifies the qualification of other audiologists at their site to assist with audiologic evaluation. Trains these audiologists and review all results for compliance with the protocol.

3) Maintains files with general information regarding the site, the protocol, and the qualifications of audiologists at their location as well as specific worksheet information on each audiologic evaluation.
4) Verifies whether each participant is audiologically eligible for entry into the study.
5) Maintains regular contact, including monthly conference calls, with the Senior Study Audiologist regarding audiology issues.
6) Promptly advises the local CRC, Clinical Site PI, and the Senior Study Audiologist as appropriate of any adverse events, concerns, or suggestions.

15.5.3 Data Management Center

The Cooperative Studies Program Coordinating Center at the Hines VA Hospital in Hines, IL, serves as Data Management Center for the SSNHL study. It is organized with a directorate coordinating the operations of the functional units shown below. The PI, Deputy Director, the Project Coordinator, and the Unit Chairs, comprise the Data Management Center directorate, which is responsible for overseeing the other units and coordinating operations with the Steering Committee. The directorate translates administrative policy decisions into general operational policies for trial conduct, and is also responsible for deciding how staff effort will be allotted among the different units.

The four organizational units are:

Administrative Unit:	Domenic J. Reda, Ph.D, Chair
Operations Unit:	Domenic J. Reda, Ph.D., Chair
Programming Unit:	Helen Shi, M.S., Chair
Analysis Unit:	Helen Shi, M.S., Chair

Regular weekly meetings of the directorate and all key staff members at the Data Management Center are scheduled. The agenda for each meeting includes reports from the director of each functional unit on progress and current problems, and a report by the Director on the activities of the Steering Committee and other project developments. The organizational units meet regularly, as required.

The Data Management Center will have primary responsibility for data collection and management. Its staff will collect, edit, store, and analyze data generated by the Clinical Sites. It will also provide key assistance in designing the data collection system and be responsible for developing and monitoring data quality control.

Additional responsibilities of the Data Management Center include:

1) Assisting the Study Chair's personnel in preparing (with the aid of the Steering Committee and NIDCD Project Scientist) the forms and the MOP;
2) Developing the experimental statistical design of the study;
3) Working with the investigators in the development and pretesting of forms and procedures, and assuming responsibility for the reproduction and distribution of forms to be used in the study;
4) Training CRCs and Lead Audiologists to monitor clinic performance;
5) Managing quality control aspects associated with the collection and management of data;

6) Summarizing Clinical Site performance, at approximately six-month intervals, for the Steering Committee;
7) Providing detailed reports regarding participant recruitment, data collection activities, and interim results to the DSMB; and
8) Assisting the Study Chair in preparing, in collaboration with the clinical site investigators, various manuscripts of the study results.

15.5.3.1 PI of Data Management Center/Study Biostatistician's Responsibilities

1) Is responsible (along with the Study Chair) for the general scientific conduct of the study
2) Collaborates with the Study Chair's Office in the development of forms and the MOP
3) Develops computer programs to monitor participant accrual, visits, and completed forms; to edit the data; to prepare interim and final statistical reports; and to perform additional statistical analyses as required
4) Establishes and maintain a participant data file for the study and run the file through the developed programs periodically throughout the course of the study
5) Develops computer programs that generate randomization lists and participant visit schedule lists
6) Supervises data coordinator
7) Contacts the Study Chair concerning problems with participant accrual, timely follow-up visits, and missing or inaccurate data forms
8) Performs site visits to centers as needed
9) Works closely with the Study Chair in planning the statistical analyses and in preparing newsletters, interim reports to the DSMB and final reports.
10) Prepares the data and statistical sections of any resulting publications. Helps interpret the data and write the results and conclusion sections of publications. Is responsible for documenting and archiving materials at the conclusion of each study according to Cooperative Studies Program guidelines
11) Prepares Executive Summary and Impact of Proposed Study Protocol Amendment

15.5.3.2 Project Manager's Responsibilities

1) Assists Study Chair's personnel in development of case report forms and the MOP
2) Maintains log of SAEs occurring during the study
3) With Senior CRC, trains site personnel in data collection and submission, and correction procedures
4) Along with the Senior CRC, maintains files of necessary approval documents, approved informed consents, and training certifications; and
5) Assists in preparing reports for DSMB meetings.

15.5.3.3 Data Coordinator's Responsibilities

1) Photocopies and distributes full sets of study forms, protocols, MOPs – all versions and updates
2) Mails out additional forms as needed by sites
3) Logs in and edits forms, reviewing for accuracy and completeness. Organizes data

for data entry and assigns codes to open ended fields
4) Works with CRCs on problems, questions or potential errors concerning the completed data forms
5) Sets up and maintains filing system for participant files
6) Fields questions on data management and query reports. Works with CRCs to resolve problems that arise on query reports
7) Sets up and maintains all binders and appropriate blanks for study, i.e. Randomization Book, Consent Book, Master List Book, Follow-up Visit Schedule Book, Randomized Participants Book, Log-in Book
8) Assists the Study Chair's personnel in arranging study meetings

15.5.4 Steering Committee

The Steering Committee will be the main governing body of the study. Membership of the Steering Committee will include the Study Chair, Data Management Center PI, the Study Senior Audiologist, the Clinical Site PIs and the NIDCD Project Scientist. All major scientific decisions will be determined by vote of the Steering Committee. Except for the organizational period, the Steering Committee will meet approximately semi-annually and have monthly conference calls.

Subcommittees of the Steering Committee will be established as needed by the Steering Committee. The NIDCD (or its designee) will have a representative on such committees.

Specific functions of the Steering Committee include:

1) Determining the scientific aims of the study;
2) Establishing participant eligibility requirements;
3) Developing the study design;
4) Developing the protocol and participating in the development of study forms and the MOP;
5) Overseeing the implementation of the protocol;
6) Establishing subcommittees and task forces, as needed;
7) Serving as the scientific forum for the study for reviewing and reporting data;
8) Making budgetary decisions;
9) Approving all ancillary study proposals; and
10) Monitoring overall study quality control.

The Steering Committee will coordinate the development of the protocol for data collection and will provide a continuous review of quality control. It will also monitor the publishing of results, determining whether a methods/baseline manuscript will be prepared, assigning priorities to the publishing of study results, assigning investigators to writing groups, determining the content and form of the presentation of final study results, settling issues regarding authorship, and reviewing and approving manuscripts before they are submitted. The Steering Committee in collaboration with the Program Office of the NIDCD will also set protocol for the ownership and final disposition of data.

15.5.5 Executive Committee

The Executive Committee will monitor day-to-day operations related to the conduct of the study, and, as appropriate, will make decisions on behalf of the Steering Committee. Such decisions, however, will be subject to the concurrence of the Steering Committee membership. The Executive Committee will consist of the chair of the Steering Committee, Data Management Center PI, the Study Senior Audiologist, and the NIDCD Project Scientist.

15.5.6 The NIDCD Office

The NIDCD is the primary funding source for the SSNHL study. Its Project Scientist will be a voting member of the Steering Committee, and other members of NIDCD may be invited to attend meetings. The NIDCD Program Office has ultimate oversight of the SSNHL study.

15.5.7 Data And Safety Monitoring Board

The members of the DSMB are appointed by the NIDCD. The DSMB acts in a senior advisory capacity to the NIDCD on policy matters for the duration of the study and will evaluate the study protocol. The DSMB meetings are attended by the NIDCD Project Scientist, the Study Chair, and the PI of the Data Management Center. Meetings of the DSMB will be called by NIDCD at least two times per year.

Specific responsibilities of the DSMB include:

1) Conducting in-depth reviews of the progress of the study at six-month intervals (which will include evaluating participant recruitment and adherence to the protocol);
2) Recommending approval for subsequent changes to the protocol suggested by the Steering Committee;
3) Reviewing outcome data and making recommendations to the NIDCD regarding continuation, modification, or early termination of the study, should it become necessary to protect the safety and welfare of the participants; and
4) Assisting the NIDCD in resolving problems referred by the PIs.

15.6 STUDY PERSONNEL

The current individuals in each position listed above can be found in Appendix A.

APPENDIX A

Personnel:

Study and Steering Committee Chair
Steven D. Rauch, MD, Massachusetts Eye and Ear Infirmary, Boston, MA

NIDCD Project Scientist
Amy Donohue, PhD, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD

Principal Investigators of Clinical Sites
Patrick J. Antonelli, MD, University of Florida, College of Medicine, Gainesville, FL
Seilesh Babu, MD, Michigan Ear Institute, Farmington Hills, MI
John P. Carey, MD, Johns Hopkins University School of Medicine, Baltimore, MD
Bruce J. Gantz, MD, University of Iowa, Hospitals and Clinics, Iowa City, IA
Joel A. Goebel, MD, Washington University School of Medicine, St. Louis, MO
Paul E. Hammerschlag, MD, New York University School of Medicine, New York, NY
Jeffrey P. Harris, MD, PhD, University of California San Diego, San Diego, CA
Gordon B. Hughes, MD, Cleveland Clinic Lerner College of Medicine, Cleveland, OH
Brandon Isaacson, MD, University of Texas Southwestern Medical Center, Dallas, TX
Daniel J. Lee, MD, University of Massachusetts Medical School, Worcester, MA
Christopher J. Linstrom, MD, New York Eye and Ear Infirmary, New York, NY
Lorne S. Parnes, MD, London Health Sciences Centre, London, Ontario, Canada
William H . Slattery, III, MD, House Ear Institute, Los Angeles, CA
Steven A. Telian, MD, University of Michigan, Ann Arbor, MI
Jeffrey T. Vrabec, MD, Baylor College of Medicine, Houston, TX

Data Management Center Principal Investigator
Domenic J. Reda, PhD, Cooperative Studies Program Coordinating Center, Hines VA Hospital, Hines, IL

Project Manager
Nancy Ellis, M.S., Cooperative Studies Program Coordinating Center, Hines VA Hospital, Hines, IL

Study Biostatistician
Helen Shi, M.S., Cooperative Studies Program Coordinating Center, Hines VA Hospital, Hines, IL

Senior Clinical Research Coordinator
Mary L. Bartley, RN., BA. Massachusetts Eye and Ear Infirmary, Boston, MA

Clinical Research Coordinators
Cathy Bathurst, RN, Michigan Ear Institute, Farmington Hills, MI
Glorimel Casambre, BS, New York Eye and Ear Infirmary, New York, NY
Sharon Congdon, Baylor College of Medicine, Houston, TX
Michelle Crespo, R.N., BSN, Cleveland Clinic Lerner College of Medicine, Cleveland, OH
Laura Eldred, University of Michigan, Ann Arbor, MI
Dorline Jean, R.N., New York University School of Medicine, New York, NY
Sharon Lindebak, MN, NP-C, University of California San Diego, San Diego, CA
Roberta Leyvas, CCRP, House Ear Institute, Los Angeles, CA
Karen Longtine, BS, RN, CCRC, University of Massachusetts Medical School, Worcester, MA
Carrie R. Reed, CRC, University of Florida, College of Medicine, Gainesville, FL

Belinda Sinks, AuD, CCC-A , Washington University School of Medicine, St. Louis, MO
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Barbara Staves, BS, CRC, University of Texas Southwestern Medical Center, Dallas, TX
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Shari Syrovy, MCl. Sc. , London Health Sciences Centre, London, Ontario, Canada
Maria Vargas, M.A. , House Ear Institute, Los Angeles, CA
Devon Weist, Au.D., University of Florida

Chair: Data and Safety Monitoring Board
Susan W. Jerger, PhD, University of Texas at Dallas

Members: Data and Safety Monitoring Board
Karen Jo Doyle, MD, PhD, University of California, Davis
Fred Gifford, Ph.D.,Michigan State University
Douglas E. Mattox, MD, Emory University
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