



Procedures for Conducting Small Arms Noise Dose Escalation Research

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14. ABSTRACT Exposure to small arms noise can cause both temporary and permanent hearing loss. The requirement to balance the prevention of hearing loss and the need for Service Member readiness, lethality, and survivability drives the design and procurement of weapons and hearing protection, health hazard evaluations, and training and operational doctrine. Damage-risk criteria (DRCs), which are algorithms used to estimate the risk posed by an exposure, should inform this balance. Modern DRCs disagree widely about the hazard posed by an impulsive noise. The current technical report describes procedures designed to identify the maximum tolerable dose (MTD) for impulse noises produced by small arms. This is a quasi-experimental dose-escalation study, wherein a noise dose is slowly increased by monotonic increases in impulse repetitions. For example, an impulse might be presented 1, 3, 8, 23, and 64 times on exposure days 1 through 5, respectively. The purpose of the procedures reported here is to identify the DRC that comes closest to predicting the empirical MTD without exceeding it.						
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Protocol Summary

Overview

Injury to the auditory mechanism can lead to hearing loss and tinnitus, which can interfere with operational communications, situational awareness and ultimately, mission success. The modern military requires talented warfighters with the necessary auditory endurance to withstand extensive and specialized training environments and to avoid force degradation during extended engagements under austere conditions. Exposure to impulsive noise from small arms is a significant risk factor for auditory injury. Numerous damage risk criteria (DRC) for impulsive noise are currently available. DRCs are algorithms that predict the allowable number of rounds (ANOR) for a given impulsive stimulus before unacceptable risk of auditory injury occurs. A practical challenge is that the ANOR for a given exposure varies widely across different DRCs, indicating a lack of clarity regarding the injury risk from small arms impulsive noise. This protocol provides a path to resolve this issue by outlining a small arms noise dose escalation study that will prospectively identify the most appropriate DRC for quasi-free field and reverberant environments. Other exposure environments will be tested as resources allow. Human research volunteers (HRVs) will be exposed to an escalating dosage of impulsive noise by increasing the number and sound level of impulsive stimuli. The numbers of exposures will be escalated within groups (across days). The sound energy levels will be escalated across groups unless the primary endpoint is observed at a lower level. The primary measure endpoint, or maximum threshold dosage (MTD), is defined as a post-exposure temporary threshold shift (TTS) in the exposed ear of ≥ 25 decibels (dB) at any stimulus frequency from 0.5 - 8 Kilohertz (kHz) or a TTS of at least 15 dB at any stimulus frequency from 0.5 - 8 kHz that has not recovered within 24 hours following exposure. Additionally, measures of non-threshold related hearing function, bothersome tinnitus, balance, and neurocognitive function will be monitored throughout the study to facilitate secondary analyses and detect adverse events. Exposure levels presented to HRVs will be chosen to exploit differences across DRCs and allow recommendation of the DRC returning the ANOR closest to the MTD without exceeding it. This study is highly relevant because the current assortment of auditory injury models without prospective or comparative validation produce an untenable status quo, wherein the same impulse can be seen as either highly hazardous or trivially hazardous, depending on the DRC used. The results of this project will inform acquisition, training, and doctrine regarding the impact of small arms impulsive noise on auditory injury.

Schedule of Events

The study protocol is designed to be completed within a five-year time frame. Timelines associated with the major milestones are outlined in Figure 1. Year one will be devoted to acquisition and installation of test equipment, refinement of data collection and analyses processes, recruitment, hiring and training of personnel and attaining necessary authorizations to recruit and enroll HRVs. Years two, three, and four will involve HRV recruitment, enrollment, and data collection with continuous assessment of results. The final year of the protocol will include completion of data collection, final data analysis, a recommendation for the most appropriate DRC for impulsive noise, dissemination of findings in DTIC reports and peer-reviewed publications, and exam site closure and restoration.

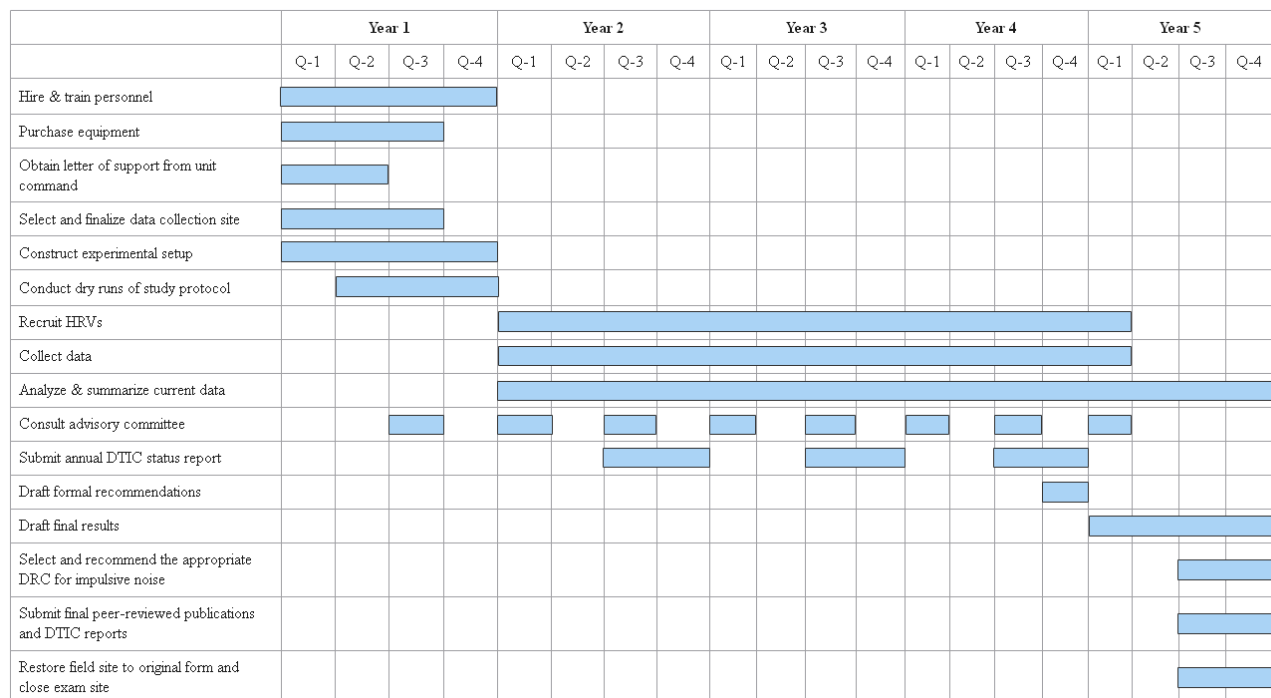


Figure 1. Major milestones associated with study protocol.

Background and Rationale

The hearing mechanism and its vulnerability to injury.

The auditory system is a complex structure that converts acoustic energy (i.e., sound) into neural activation patterns that listeners perceive as sound (Figure 2). The pinna of the outer ear directs ambient acoustic energy through the ear canal to the tympanic membrane, which converts the sound waves into mechanical vibrations. These vibrations are amplified and transmitted through the middle ear via the ossicular chain to the oval window of the cochlea, setting the basilar membrane of the cochlea into motion which, in turn, is transduced by hair cells into electrical potentials which stimulates the auditory nerve (Pickles, 2008).

Sound can also serve as an agent of injury to the auditory system. High-level sound blasts can traumatize the tympanic membrane and related structures leading to compromised energy conduction through the middle ear mechanism. Recovery is dependent upon the details of the trauma but is often reversible. More insidious to long-term hearing health is noise-related injury to cochlear structure and function (Kryter, 1985). Acute and chronic noise exposure is known to result in damage and/or death of cochlear hair cells (Cody & Russell, 1992). More recently, animal studies have demonstrated that noise exposure can impact the density of synaptic connections between hair cells and dendrites of the auditory nerve (Kujawa & Liberman, 2009; Liberman, Suzuki, & Liberman, 2015). Sensorineural injuries are associated with reduced hearing sensitivity, sound localization, speech recognition and sound discrimination within noise, and tinnitus (Ward, Royster, & Royster, 2000). For some exposures, the functional impact appears temporary with a return to normal function over the course of minutes to days (Chan,

Ho, & Ryan, 2016; Kryter, 1985; Ward, 1960). Most concerning are exposure-related injuries that interfere with readiness or lead to permanent changes in auditory function.

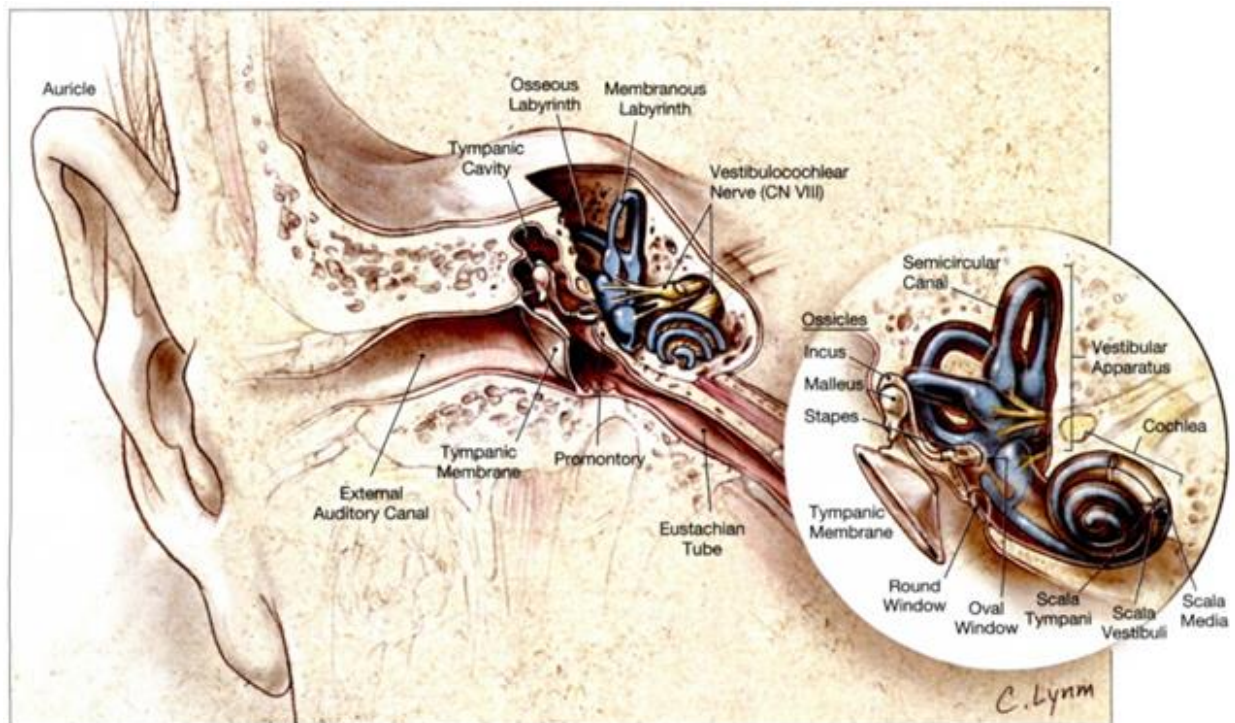


Figure 2. Anatomy of the external, middle, and inner ear (Yueh, Shapiro, MacLean, and Shekelle, 2003).

Small arms noise is a risk factor for hearing injury and force readiness.

The impulsive noise produced by small arms fire has been considered a major hearing loss risk factor for many years (Murray & Reid, 1946). Even occasional exposure to impulsive noise from small-caliber hunting weapons has been shown to be strongly related to permanent noise-induced hearing loss (Nondahl et al., 2000). A DRC is an auditory injury model that links acoustic exposure to the risk of an auditory outcome. Although a number of DRCs currently exist for impulsive noise, a detailed understanding of the relationship between the number and type of impulsive exposures from small arms fire, and the risk of auditory injury, is lacking. This gap in knowledge impacts decision-making in many areas of the military, including weapons design, training, and operations. All Service Members are exposed to small arms fire during Initial Entry Training (IET). Training-related small arms exposure after IET will vary widely across military occupational specialties (MOSs), yet all Service Members participate in ongoing small arms training and qualification throughout their career (Department of the Army, 2019b). Therefore, training-related small arms noise exposure is a significant risk factor for the trainee and the personnel that oversee training and qualification. DRCs are also used to identify the minimum safe distance for unprotected personnel at firing ranges. The locations of observation and staging areas relative to the firing line are informed by the DRCs in use at the time of range construction. Recent training guidelines explicitly aim to match training as closely as possible to operations (Department of the Army, 2019b). Excessively restrictive exposure guidelines during training could delay or compromise the development of important skills, so it is critical for small arms

training to minimize hazard while optimizing readiness. Conversely, training operations need to occur with the confidence that the warfighter's health, performance, capacity for deployment, and operational readiness are not negatively impacted by excessive exposure. During operations, noise-related hearing injuries are threats to maximizing force capacity because they interfere with communications, situational awareness (Price, Kalb, & Garinther, 1989) and, ultimately mission success (Fedele, Weatherless, Kehring, & Letowski, 2013; Sheffield, Brungart, Tufts, & Ness, 2017).

Linking impulsive noise exposure to hearing injury: Historical studies.

The formative research assessing the effects of small arms impulse noise on auditory risk in humans date back to the 1950s and 1960s (Coles, Garinther, Hodge, & Rice, 1967). The impact of these studies cannot be overstated as they led to the development of a DRC, adopted by MIL-STD 1474A-D, which informed military decision-making for more than 40 years until 2015 when MIL-STD 1474E was promulgated. There is no doubt that (Coles et al., 1967) was a significant step forward. However, the technological limits of the era obligated the use of time domain measures that could be made with an oscilloscope: peak pressure level, the duration of the pressure wave (A-duration) and the duration of the envelope (B-duration). These parameters had a lasting influence on impulse noise measurement, perhaps because they are the only durable records of these early studies. Audio recording limitations at the time precluded the application of modern signal processing options, such as spectral or kurtosis analysis.

There are other factors that limit use of the (Coles et al., 1967) and related data for modern DRC validation. Damage risk limits were estimated using functions relating peak pressure to A- and B-durations. The risk isocontour has a straight-line component at longer B-durations with a slope derived using firing data from only two conditions, the 7.62 x 51 millimeter (mm) North American Treaty Organization (NATO) rifle in a quasi-free field and the mean of two rifles (.303 and .22 caliber) in a reverberant environment. The development of a contour based on two points is problematic because the form of the relationship between those points cannot be specified. This problem is magnified because the slope of the contour was extrapolated well beyond the measured range. Thus, this DRC's generalizability to novel waveforms is uncertain. Additionally, the hearing sensitivity of the participants in the studies contributing to Coles et al. (1967) would not be considered normal using current standards, which is particularly problematic because hearing sensitivity is known to influence noise-induced TTS (Humes & Jesteadt, 1991), and TTS was the only outcome measure employed in these studies. No other measures of hearing function were reported, negating the opportunity to assess hearing function in the absence of TTS, an area of growing research interest (Guest, Munro, Prendergast, Howe, & Plack, 2019). Finally, MIL-STD 1474A-D included a fixed 29 dB reduction in peak level for single hearing protection, based on the measures from a shoulder-fired rocket launcher (Garinther & Hodge, 1971), and an additional 6.5 dB reduction if double protection (combined earplug and earmuff) was used. Such a standard is overly simplistic given the wide range of hearing protectors available to military personnel and is inconsistent with recent studies that indicate that single hearing protection provides an average of 11 dB (range: 3 to 27 dB) of greater protection than predicted (Gallagher, McKinley, Theis, & Bjorn, 2014).

The auditory risk estimates based on small arms included in MIL-STD 1474A-D have questionable generalizability to large caliber weapons due to the spectral properties of the large weapons blasts and the hearing protection worn by weapon operators (Patterson et al., 1985; Price, 1982). The need for more widely applicable risk estimates for impulse noise led to the development of auditory risk models that can accommodate novel waveforms (Price, 2007) and prompted a human and animal exposure study using blasts similar to large caliber weapon noise. Known as the Blast Overpressure Study (BOP) (Johnson, 1993), the aim of the study was to “walk up” or escalate the impulse noise dose by increasing the energy level and number of blast exposures to hearing-protected participants while assessing for evidence of TTS. As with the work of Coles et al. (1967), the BOP study was a well-designed study for its time, but suffers some limitations. Strengths include the use of participants that were early in their military careers and therefore, had greater uniformity in exposure history. In keeping with conventional dose escalation designs, participants also stayed in a common residence for the duration of the study, thus allowing a degree of control and monitoring of non-experimental noise exposure. On the other hand, similar to the previous small arms work, non-threshold hearing measures such as assessment for tinnitus or measures thought to reflect cochlear synaptopathy were not included. Additionally, the study was not designed to generalize beyond the longer-duration impulse waveforms associated with large blasts. An unexpected outcome of the BOP study was that, when wearing hearing protection, the number of participants exhibiting TTS was less than expected, making it difficult to identify the boundary between safe and unsafe blast exposures. As a result, performance-degrading adjustments were made to the protectors, which resulted in greater TTS but at the cost of uncertainty about the nature of the exposure levels to participants and generalizability to signals that might be hazardous with protectors as they would be used in practice. Evidence that hearing protectors exceed predicted protection from noise injury (Gallagher et al., 2014) is consonant with the results of the BOP study. The reason for this additional protection effect is not well understood, but may be related to the shape and size of the ear canal, acoustic impedance of the tympanic membrane that may vary with level of canal occlusion, occlusion-related changes to ossicular chain and acoustic reflex dynamics, and/or reductions in the stress reaction (Gallagher et al., 2014).

Linking impulsive noise exposure to risk of auditory injury: Damage risk criteria (DRC).

Since these historical studies, a number of DRCs have been developed for impulsive noise. DRCs can be categorized based on whether they are determined by waveform parameters (e.g., peak and envelope duration) (Ward, 1968), integrated waveform energy (Atherley & Martin, 1971; Chan et al., 2016; Chan, Ho, & Zagadou, 2018; DTAT, 1983), or complex mathematical models meant to represent auditory physiology (Price, 2007; Zagadou, Chan, Ho, & Shelley, 2016). The differences across DRCs can be expressed in the common unit of the ANOR. The colored curves in Figure 3 plot the ANOR as a function of A-weighted integrated energy level for common DRCs. The general shape of the curves is similar, indicating that the different DRCs produce correlated outcomes. However, the location of the different DRC curves along the abscissa vary substantially, which indicates that the ANOR for a given impulsive stimulus can vary greatly across DRCs (Flamme, Liebe, & Wong, 2009; Flamme et al., 2019; Flamme, Wong, Liebe, & Lynd, 2009). Disagreements across DRCs regarding ANOR are a considerable problem for the users of these models, who are frequently obligated to judge

whether an impulsive sound is safe. For example, an impulse with an integrated energy level of 50 dBA returns ANORs that range from as few as 7 impulsive stimuli (Integrated Cochlear Energy (ICE), assuming no acoustic reflex) to as many as 102,338 impulsive stimuli (off scale, Coles/CHABA). At least one of these estimates is incorrect and likely by a very large margin. The wide range in ANORs implies that the use of an inaccurate DRC will either result in significant hearing injury or set a limit so restrictive that it unnecessarily constrains training and operational flexibility. Despite the lack of confidence this inspires in users of the DRCs, the divergence affords an opportunity to make unambiguous comparisons of DRC predictions against an empirically-derived MTD. It is fortunate that the divergence occurs at low impulse energy levels, where the hazards posed to listeners can be minimized through a careful dose-escalation regime. To address this untenable situation, this report outlines a dose escalation study that will prospectively determine which, among the current candidate DRCs, provides the ANOR that best describes the MTD for a group of stimulus classes relevant to small arms weapon exposures.

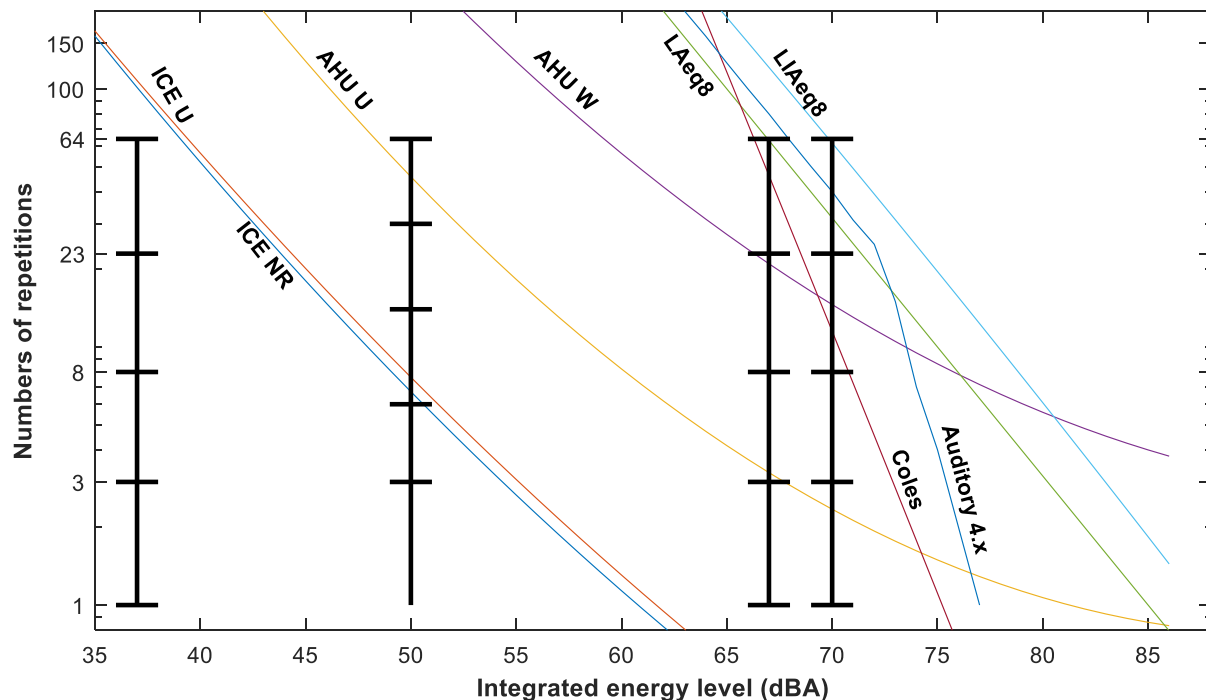


Figure 3. Number of repetitions of impulsive stimuli plotted as a function of integrated energy level (dBA) for small arms impulses in a quasi-free field. Each colored line represents the calculated ANOR for current candidate DRCs. This also includes an example set of four dose escalation series for the quasi-free field stimulus class. The vertical bar near 37 dBA represents the reference/control stimulus class, which is not expected to produce a criterion TTS by any candidate DRC. The remaining vertical bars represent energy levels that may be used in the dose escalation. ICE NR=Integrated Cochlear Energy, no acoustic reflex; ICE U= Integrated Cochlear Energy, unwarned; AHU U=AHAAH Auditory Hazard Units, unwarned; AHU W= Auditory Hazard Units, warned; LAeq8=A-weighted 8-hour equivalent continuous level; LIAeq8= Impulse-adjusted A-weighted 8-hour equivalent continuous level; Coles et al., 1967/CHABA 1968 rule; Auditory 4.x= Auditory 4.0 model.

Eight variants of six different candidate DRCs will be assessed. The Auditory Hazard Assessment Algorithm for the Human (AHA AH) (Price, 2007) is one of two DRCs included in MIL-STD 1474E (US Department of Defense, 2015). AHA AH employs an electro-acoustic model of the auditory pathway intended to conform to ear anatomy and physiology. The constituents of the outer, middle and inner ear are modeled separately, giving rise to a large number of model parameters and considered by the model developers to provide the advantage of deeper insights into the function of the ear. The model also contains non-linear elements of the conductive path including a potentially protective role for the middle ear muscle contraction (MEMC) as well as limits to stapes displacement due to the annular ligament. AHA AH represents dose in terms of Auditory Hazard Units (AHU), which are based on modeled displacements at distinct locations along the length of the basilar membrane. Only the basilar membrane segment with the greatest integrated upward displacement is represented in the AHU. Warned and unwarned versions of the AHA AH model will be tested, differing only in the role of the MEMC. The unwarned version only assumes a reflexive MEMC, which, due to response lags, plays no protective role for single impulsive exposures, whereas the warned version assumes a fully engaged MEMC prior to impulse onset (Price, 2007). The inclusion of MEMC in AHA AH has been a source of considerable debate since its inception, and recent studies have demonstrated that MEMCs, either in response to, or in anticipation of impulsive sounds, are not pervasive phenomena in listeners with very good hearing (Deiters et al., 2019b; Flamme, Deiters, Tasko, & Ahroon, 2017; McGregor et al., 2018).

Integrated Cochlear Energy (ICE) (Zagadou et al., 2016) builds on the biomechanically-based AHA AH model with modifications including a number of parameter adjustments to better represent human data, annular ligament parameter optimization to eliminate a dose-response inversion occurring in AHA AH at high exposure levels, and calculating integrated cochlear energy rather than AHU based on basilar membrane displacements as the dose metric. A dose-response curve was developed using ICE based on existing data from small arms (Coles et al., 1967), large weapons (Johnson, 1993), and measures made with an artificial test fixture. An unwarned version (ICE U, analogous to unwarned AHA AH) and a version with no early or reflexive MEMC (ICE NR) will be tested.

Auditory 4.0/4.5 (Chan et al., 2016) is an empirically-derived impulsive noise injury model based on historical human data on rifle noise exposure (Coles et al., 1967) and heavy weapons noise exposure (Johnson, 1993) as well as both historical (Hamernik & Ahroon, 1998; Hamernik, Ahroon, Jock, & Bennett, 1998) and acquired data from chinchilla (Chan et al., 2016). It is unique among candidate DRCs because it estimates human dose-response curves and predicts impulsive noise risk for a wide range of TTS and PTS injuries in unprotected ears. This model also includes predictions of recovery from TTS based on observations made with chinchilla.

The 8-hour equivalent A-weighted energy (LAeq8) model (Atherley & Martin, 1971) and related LIAeq8 represent DRCs based on estimated impulsive waveform energy. LAeq8 is currently used by the European Union, and its variant, the LIAeq8, is included in MIL-STD 1474E (US Department of Defense, 2015). The difference between LAeq8 and LIAeq8 is that LIAeq8 relaxes exposure limits for waveforms with long pressure-wave durations, such as large caliber weapon systems.

The final DRC under consideration is that proposed by (Coles et al., 1967), described earlier, which calculates risk using a function relating peak level and A- and B- durations of the impulsive waveform and was used in MIL-STD 1474D (US Department of Defense, 1997) and its predecessors. This DRC was developed using TTS responses to small arms noise using collective results from hundreds of unprotected human listeners. It is considered a candidate DRC in this research due to its historical significance and because it is reasonable to expect some lawful relationship between the empirical results leading to this DRC and the prospective observations made in this research.

Research approach: Dose Escalation Study.

The current study protocol is designed to identify the MTD for impulsive noises similar to those produced by military small arms. It emulates a dose-escalation research design employed in Phase I clinical trials to assess toxicity of pharmaceutical agents (Korn et al., 1994; Le Tourneau, Lee, & Siu, 2009; Storer, 1989). A dose escalation study gradually increases the dosage level of a test agent while assessing the primary outcome to identify the onset of toxicity, the MTD. The MTD is the estimated toxicity level deemed to carry an unacceptable risk of harm. In most pharmaceutical dose-escalation studies, a balance must be struck between the goal of reducing the likelihood of toxicity and expanding the range of doses available to eventual users of the drug. These conflicting objectives lead to designs that often expose significant numbers of people to toxic doses (Iasonos, Gönen, & Bosl, 2015). In the context of the current study, there is no inherent advantage in administering noise doses beyond the level necessary to distinguish the optimal DRC. As described below, the identification of the targeted outcome in a human Research Volunteer (HRV) halts additional exposures at or above that level. In the current study protocol, the exposure agent is an impulsive sound stimulus generated from firing a small arms blank cartridge with known waveform characteristics. Subgroups of 4 HRVs will be seated around the impulsive sound source at a distance known to provide a desired range of ANORs returned by candidate DRCs. Daily exposures will be presented with the number of repeated impulsive stimuli ascending each consecutive day, up to a maximum of five exposure days (64 repetitions). The ascending exposure sequence is designed to optimize between maximizing the differentiation of each DRC (based on ANOR predictions) and graduating the dose escalation to mitigate risk due to overexposure. Because the range of ANOR associated with each DRC varies significantly for different impulsive levels or types, a single dose escalation series might not be sufficient to identify the MTD. Instead, dose escalation series will vary by impulsive stimulus level (e.g. 50, 67, 70 dB LAeq8) and stimulus class (e.g., quasi-free field, low and highly reverberant environments, simultaneous/sequential impulsive exposures, mixed sound sources, etc.).

Exposure to intense or repetitive impulsive noise can result in temporary or permanent changes in hearing thresholds. A temporary threshold shift (TTS) is a threshold shift characterized by a gradual return to baseline hearing sensitivity that can take from minutes to days (Chan et al., 2016). In general, the larger the TTS, the greater the recovery (Chan et al., 2016; Ward, 1960). However, the increase in recovery rate does not fully compensate for the magnitude of the TTS, so recovery time increases with TTS magnitude (Chan et al., 2016; Kryter, 1985; Ward, 1960). A noise-related permanent threshold shift (PTS), by definition, does

not return to pre-exposure hearing sensitivity leading to permanent reduction in hearing sensitivity. DRCs are designed to assess risk for permanent auditory injury (i.e., PTS). Because TTS occurs at lower exposure levels than PTS and is temporary, it has been used as an early indicator of permanent hearing injury (Coles et al., 1967; Johnson, 1993; Kryter, 1985). For example, the Albuquerque BOP Study assessed risk of auditory and injury to air-filled organs (e.g., lungs, trachea) to large weapon blasts using a TTS of 25 dB, averaged across 1, 2 and 4 kHz, as the criterion for study endpoint (Johnson, 1993). Sample size was determined so that a single HRV that met or exceeded the criterion TTS stopped the dose escalation series because it exceeded the 5 percent likelihood of observing the criterion TTS within the study population. Thus, the risk of HRVs meeting criterion TTS was relatively small. The current study protocol uses the same methods as the BOP study for determining sample size, to reduce the likelihood of HRVs experiencing criterion TTS. However, the criterion TTS will be more conservative than for the BOP study. The endpoint for a dose escalation series will be a TTS of ≥ 25 dB at any test frequency between .5 and 8 kHz measured 2 minutes post-exposure series, or a TTS that is ≥ 15 dB and < 25 dB measured 2 minutes post-exposure series that has not returned to baseline hearing sensitivity within 24 hours following the exposure.

In addition to assessment for TTS, measures reflecting changes in tinnitus, balance/vestibular function and threshold-independent measures of auditory function will also be closely monitored throughout the dose administration series since all are potentially impacted by noise exposure. Threshold-independent measures of auditory function are of particular interest since studies using a range of non-human mammalian species have demonstrated noise-related reductions in density of ribbon synapses between inner hair cells (IHC) and spiral ganglion neurons (SGN) in the absence of a measurable threshold shift (Kujawa & Liberman, 2009). This damage, referred to as cochlear synaptopathy, appears to preferentially affect high-threshold, low spontaneous firing rate neurons (Furman, Kujawa, & Liberman, 2013; Valero, Hancock, Maison, & Liberman, 2018), which is consistent with the preservation of normal hearing thresholds in quiet. The ribbon synapse density reductions can persist long after exposure, eventually leading to SGN death and threshold shift (Kujawa & Liberman, 2009). There is evidence that damage may be reversible, at least in strains and species of laboratory animals (Lin, Furman, Kujawa, & Liberman, 2011; Shi et al., 2013), and there is a possibility that pharmaceutical agents could facilitate the restoration of these connections (Seist et al., 2020).

Most animal studies employ continuous noise exposure and criterion TTS magnitudes far in excess of those used in human research, so the role of impulsive noise on cochlear synaptopathy in humans is not well understood (Guest, Munro, Prendergast, Howe, & Plack, 2017; Guest et al., 2019). The presence of noise-induced cochlear synaptopathy in laboratory animals has led to speculation about a possible role in human hearing function, which complements common complaints of difficulty understanding speech in noise and the presence of tinnitus in the absence of threshold shifts (Liberman, Epstein, Cleveland, Wang, & Maison, 2016). However, generalization of results from animal models with uniform genetics and established noise exposure histories is not straightforward. Confirmation of synaptopathic change requires post-mortem analysis, and it is not possible to confirm synaptopathy in living humans (Bramhall et al., 2019; Bramhall, McMillan, Kujawa, & Konrad-Martin, 2018). Therefore, indirect approaches must be used in humans to assess for evidence of auditory disturbances in the absence of threshold shifts (Liberman et al., 2016; Mepani et al., 2020).

These studies have led to a growing list of candidate measures including measures of speech understanding in degraded conditions (Fulbright, Le Prell, Griffiths, & Lobarinas, 2017), hearing thresholds at high frequencies (Liberman et al., 2016), magnitude (Liberman et al., 2016; Ridley, Kopun, Neely, Gorga, & Rasetshwane, 2018; Stamper & Johnson, 2015) and latency (Mehraei et al., 2016) of electrocochleography (ECoChG) and auditory brainstem responses (ABR), distortion product otoacoustic emissions (DPOAE) (Bramhall et al., 2018), characteristics of MEMCs (Kamerer, Kopun, Fultz, Neely, & Rasetshwane, 2019), and perception of frequency modulated signals (Kamerer et al., 2019). In spite of this progress, there is no current evidence that the human auditory system is more sensitive to synaptopathy than it is to the criterion TTS, which is the primary outcome for the current study. Indeed, some investigators have determined that the research on human synaptopathy is inconclusive and has yielded results inconsistent with expected synaptopathic effects (Prendergast et al., 2019). Because of this uncertainty, the current study will employ extensive testing of auditory status before and after each exposure series to monitor for acute changes in auditory status that would be consistent with synaptopathy and synaptopathy is included as a possible adverse effect for this study design.

Hearing and neurocognitive function as a function of impulsive noise exposure.

Shock waves associated with blasts from large caliber weapons and explosive devices can be injurious to a wide range of body systems. Warfighters who survive acute blast-related injuries are still at high risk for long-term functional impact due to concussion/traumatic brain injury and auditory system damage. Even brief, less intense impulsive stimuli may impact neurocognitive function in measurable ways that affect operational effectiveness (Caplan et al., 2010; Sajja et al., 2019). Although auditory damage affects the health and readiness of the warfighter in its own right, the comorbidity between auditory damage and brain trauma for blast-related injuries positions measures of auditory function as a potential leading indicator of neurocognitive changes, which may develop according to a different timeline. The association between measures of hearing and measures of neurocognitive function is not well understood. The proposed study will address this knowledge gap. In addition to pre- and post- noise exposure measures of hearing function, neurocognitive function will also be assessed using the Defense Automated Neurobehavioral Assessment (Lathan, Spira, Bleiberg, Vice, & Tsao, 2013), thus allowing for examination of associations between auditory and neurocognitive measures.

Use of Military personnel as HRVs.

The study protocol requires military personnel as HRVs. Clinical research supported by the U.S. Department of Defense is required to include members of the Armed Services, women, and members of minority groups as participants (United States, 103rd Congress, House, & Committee on Armed Services, 1994), unless a waiver of this requirement would be appropriate. The current study is needed to inform the selection of a DRC for use by the U.S. Armed Forces. An early-career military population is the optimal population for sampling because candidate DRCs were specifically developed to mitigate auditory injury for military personnel. Additionally, military and civilian populations differ in a number of ways that can limit the generalizability of results.

Although exposure to small arms fire varies greatly across different MOSs, all Service Members engage in intensive small arms training during Initial IET (Department of the Army, 2019c) and to maintain readiness thereafter. Since marksmanship skills are perishable, Service Members complete weapon qualifications (including training if necessary) throughout their career at intervals dictated by small arms training and qualification standards (Department of the Army, 2019b). Data from the National Health and Nutrition Examination Survey (NHANES), a complex multistage survey of the civilian non-institutionalized U.S. population, was examined for firearm use. Using a civilian age group similar to those entering IET (18-29 years), results indicate that about 42 percent of males and only 15 percent of females reported having ever used a firearm (K. Deiters, personal communication, August 13, 2020). Even for the minority of civilians who regularly use firearms, the types of firearms, training, and exposure patterns differ substantially from military doctrine. Additionally, stress reaction associated with high-level noise exposure may serve to modulate degree of noise-induced TTS (Gallagher et al., 2014), supporting use of military personnel, who are trained to perform duties in noisy environments. Military personnel constitute a more homogeneous group in terms of the training received, the firearms used, impulsive exposure histories, and comfort around high-level noise.

There is evidence that cardiovascular fitness may serve a protective function for hearing. Small group and correlational studies indicate young adults with high cardiovascular fitness exhibit less noise-induced TTS than those with lower fitness levels (Kolkhorst et al., 1998; Manson, Alessio, Cristell, & Hutchinson, 1994). Additionally, a large-scale analysis using NHANES data found that cardiovascular health was positively associated with hearing sensitivity (Loprinzi, Cardinal, & Gilham, 2012). Rigorous physical training is a common component of IET and military personnel are required to meet physical fitness standards on a regular basis (Department of the Army, 2019c). There is evidence that military personnel exhibit a greater, and more consistent level of physical fitness than the civilian population. Recruits entering service have a lower body mass index (BMI) values (Knapik, Redmond, Grier, & Sharp, 2018; Knapik, Sharp, & Steelman, 2017) than a non-military population with a similar age group (K. Deiters, personal communication, August 13, 2020). Although BMI is not an optimal measure of fitness, secular changes in BMI does covary with more direct measures of fitness (e.g., two-mile run times).

Due to these factors, civilians may be more likely to exhibit a criterion TTS, which could lead to an underestimate of the MTD for a military population and, ultimately, to an unnecessarily restrictive DRC. An unnecessarily restrictive DRC could negatively impact doctrine, training and, ultimately, force readiness.

Military Relevance and Impact

A clear understanding of the risk of auditory injury from impulses is lacking, which compromises acquisition, training, and doctrine. Success in today's multi-domain battlespace depends on maximizing warfighter's capability to secure mission objectives in highly contested environments, potentially requiring extended contests for control of physical space and effective operation in austere environments. A failure to manage the balance of weapon lethality and operator injury can lead to excessive re-assignment and retraining rates, especially among elite warfighters and the Service Members who train them (e.g., firing range personnel). The expertise

and endurance required of our warfighters implies the need to attract, train, and most importantly retain personnel with high levels of resilience and capacity (U.S. Army, 2018), therefore providing short- and long-term positive impact on warfighter operational success. The expanded modern battlefield is increasingly lethal and hyperactive, and current modernization efforts (U.S. Army, 2019) must be informed by the warfighter's capacity to endure and perform effectively during training scenarios or conflict involving high-tempo and extended operations.

This study will identify the DRC that provides the largest ANOR without exceeding the MTD across a range of exposure environments. The data to be collected is necessary for the validation of auditory injury risk prediction models used to inform health hazard assessment and results will be used to inform design and acquisition of weapons, wearable technology, and proper protections from hearing protection devices. This study is highly relevant to military application, as the current assortment of auditory injury models without prospective or comparative validation produce an untenable status quo that prevents informed acquisition, training, and doctrine regarding the potential impact of those activities on the Service Member's hearing. The military requires a resolution of this situation.

Study Objectives

Primary Objective

The primary objective of the proposed protocol is to determine which of eight candidate DRCs for impulsive noise comes closest to the MTD without exceeding it. The candidate DRCs include one parameter-based DRC (Coles et al., 1967); three DRCs based on integrated energy (Atherley & Martin, 1971; Chan et al., 2016; U.S. Department of Defense, 2015); and two DRCs containing mathematical models (Price, 2007; Zagadou et al., 2016). Both of the mathematical models return different results depending on the assumed role played by middle ear muscle contractions. Despite evidence that middle ear muscle contractions do not provide a dependable reduction in auditory risk (Deiters et al., 2019a; Flamme et al., 2018), it is possible that the tuning of model parameters to match human TTS outcomes could yield ANORs similar to the MTDs identified in this study.

Primary Objective Endpoint

The primary objective endpoint is one or more HRVs exhibiting an MTD defined as a $TTS \geq 25$ dB TTS at any frequency between 0.5 and 8 kHz measured 2 minutes post-exposure or a TTS that is ≥ 15 dB at any frequency between 0.5 and 8 kHz that has not returned to within the 95% confidence interval of the baseline hearing sensitivity 24 hours following exposure. Meeting the criterion TTS will stop all HRVs in that cohort from being exposed to greater numbers of impulsive noise repetitions for the current energy level and any impulses at higher energy levels in that stimulus class. Risk factors and correlates of TTS will also be evaluated.

Secondary Objectives

The secondary objectives of the proposed protocol are to determine:

1. The probability of temporarily eliciting tinnitus or increasing its loudness at exposure levels that may not produce a criterion TTS. Measures used will include self-report of bothersome tinnitus and a psychophysical procedure to determine the noise level necessary to eliminate the audibility of tinnitus.
2. The probability of eliciting changes across a wide range of non-TTS hearing function, which have been used as candidate measures of cochlear synaptopathy, at exposure levels that may not produce a criterion TTS. Measures will include hearing thresholds in noise, frequency modulation threshold detection, amplitude and latencies of events during evoked response testing, and otoacoustic emission suppression.
3. The probability of eliciting changes in balance function at exposure levels that may not produce a criterion TTS. A modified Romberg Test of Standing Balance will be used to screen standing balance. Timing and accelerometer information will be used to monitor for changes in balance function.
4. The probability of eliciting changes in measures of neurocognitive status at exposure levels that may not produce a criterion TTS. Measures used will include self-report measures of headache and related symptoms and measures drawn from the Defense Automated Neurobehavioral Assessment (DANA).
5. Associations between measures of tinnitus, non-TTS hearing function, balance and vestibular function, neurocognitive status and measures of exposure-related motor activity and autonomic arousal, and criterion and non-criterion TTS. In addition to measures outlined above, during the exposure period, motor activity of the head and neck and will be monitored via surface electromyography and arousal levels will be monitored using measures of heart rate variability and skin conductance level.

Many of the variables used to evaluate the secondary objectives are also monitored for the purpose of detecting adverse events. These are described below (section 9).

Study Design Overview

This is an impulsive noise dose-escalation study designed to select the candidate impulsive noise DRC that returns the ANOR closest to the MTD without exceeding it. The operational definition of MTD is the dose that provides 95% confidence that at least 95% of exposed Service Members will be protected from a criterion TTS (operationally defined in previous section).

HRVs are divided into 7 cohorts, each containing 64 HRVs. Each cohort is divided into 8 groups of 8 HRVs, and further subdivided into subgroups of 4 HRVs. Eight HRVs will complete the study at a time, and each subgroup of 4 HRVs will complete testing together while staggering test areas with the other subgroup of 4 HRVs.

Parameters that vary by cohort include impulse energy level, stimulus class and ear canal occlusion. The occluded condition will not be evaluated until all unoccluded stimulus classes have been tested. The unoccluded stimulus classes will be evaluated before the occluded class because the uncertainties introduced by hearing protector fit, acoustic attenuation, and additional effective attenuation (Gallagher et al., 2014) would be prohibitive until some DRCs have been rejected. Members of a cohort will be exposed to only one stimulus class, impulse energy level, and occlusion condition. Each cohort will be assigned sequentially to a single stimulus class. The

study design supports the evaluation of stimulus classes 1 through 3. The remaining stimulus classes will be evaluated if one or more of the 7 planned cohorts are available for assignment to stimulus classes 4 and above. The stimulus classes are:

1. Control/reference, unoccluded
2. Quasi-free sound field, unoccluded
3. Highly reverberant sound field, unoccluded
4. Concurrent impulse + random noise sound field, unoccluded
5. Sequential random noise, then impulse sound field, unoccluded
6. Concurrent impulse + vehicle noise sound field, unoccluded
7. Occluded with hearing protector

Within a stimulus class, cohorts will be assigned to an energy level that provides the capacity to reject one or more candidate DRCs. In each stimulus class, a candidate DRC is rejected if it is too restrictive and a criterion TTS is not observed at repetitions above the ANOR of the next most restrictive candidate DRC. Additionally, a DRC is rejected for a stimulus class if its ANOR is greater than the dose level producing a criterion TTS because it fails to provide 95% confidence that 95% of exposed persons would be protected against a criterion TTS. For example, if for a given stimulus class and level, DRC “x” returns an ANOR of 12 and DRC “y” returns an ANOR of 30, DRC “x” would be rejected if there were no criterion TTS events in a cohort that had been exposed to 30 or more repetitions of the impulse. Note, however, that DRC “x” would be adopted for that stimulus class if there was a single criterion TTS event between 13 and 29 repetitions. Likewise, any candidate DRC that returns an ANOR exceeding the MTD will be rejected for that stimulus class.

ANOR values are the DRC products of interest to the current study. The propellant charge, source-receiver distance, and other environmental characteristics will be modified to generate the acoustic characteristics producing the desired scale and range of ANOR values. To the extent feasible, the ANOR for the most restrictive candidate DRC will be between 3 and 10. The ANOR for the least restrictive DRC will be a maximum of 64. The lowest number of repetitions would be 50% of the most restrictive candidate DRC, and equidistant repetitions on a logarithmic scale implies repetitions of 1, 3, 8, 23, and 64, increasing monotonically through the 5-day dose escalation series. For example, the vertical bar in Figure 3 at 50 dBA provides an example of ANORs tested each day to confirm or rule out ICE NR, ICE U, and AHU U. At this integrated energy level, the ANOR for ICE NR is 7, so the lowest number of repetitions is 3 and the intermediate points were adjusted accordingly.

The control/reference stimulus class will use a stimulus with a low energy level (≈ 37 dB LAeq8) to produce ANOR values for all candidate DRCs that are higher than the number of exposures presented (Figure 3, vertical bar furthest to the left). This stimulus class will be used to confirm that the study protocol is unlikely to yield false positive indications of reaching criterion TTS and to provide assurance that the MTD is not below the most restrictive candidate DRC.

In principle, a single dose escalation series could be used to accept or reject all but the least restrictive candidate DRC for a given stimulus class. However, the vast range of ANORs returned by contemporary DRCs limit the utility of a single energy level. In the current study,

repetitions are limited to a maximum of 64, and the ANOR can be shifted into a practical range by controlling the exposure energy to fit the target ANOR range. One or more candidate DRCs must produce testable ANORS in consecutive impulse energy levels for validation across energy levels.

If a criterion TTS is observed in a stimulus class, additional HRVs will not be exposed at or above the number of repetitions producing the criterion TTS. Also, HRVs will not be exposed to higher energy levels within that stimulus class because the MTD will have been determined. Any future HRVs that would have been assigned to a higher energy level within that stimulus class will be assigned to the next stimulus class. Using Table 1 as a hypothetical example of progression through the 67 dB energy level in the quasi-free field, groups of 8 HRVs will progress through the specified repetition schedule [1, 3, 8, 23, 64] in subgroups of 4 HRVs each. The numbers of repetitions would increase monotonically by day until the maximum number of repetitions is reached or until a criterion TTS is observed. In this example, all members of subgroups 1a and 1b progressed through 64 impulse repetitions without sustaining a criterion TTS. A criterion TTS was identified in subgroup 2a on exposure day 4 (23 repetitions), which closes escalations to 23 and 64 repetitions for group 2b and later. Another criterion TTS was identified in group 3b, closing escalations to 8 repetitions at this stimulus class and level. In this example, no HRVs sustained a criterion TTS at 1 or 3 repetitions, and the MTD for this stimulus class would be reported as 3 repetitions. In this hypothetical example, the unwarned AHAH AHU would be selected as the preferred DRC for this stimulus class (see Figure 3).

Table 1. Hypothetical Cohort Progression through a Stimulus Class.

Subgroup	Impulse repetitions				
	1	3	8	23	64
1a	4	4	4	4	4
1b	4	4	4	4	4
2a	4	4	4	4*	n/a
2b	4	4	4	n/a	n/a
3a	4	4	4	n/a	n/a
3b	4	4	4*	n/a	n/a
...	...	...	...	...	...
8b	4	4	n/a	n/a	n/a
Numbers of HRVs with criterion TTS	0	0	1	1	0
Total HRVs	64	64	32	12	8

Note: Asterisks (*) denote a case where one HRV sustained a criterion TTS, which closed cells at and above the number of repetitions. In this example, the MTD would be 3 (the greatest number of repetitions that did not produce a criterion TTS).

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Study Product (Noise Exposure Stimulus)

Description of the Noise Exposure Stimulus

Impulsive stimuli will be generated by discharging custom-made blank cartridges using a Blank Discharge Apparatus (BDA), described in the next section. Blank cartridges will be used to minimize risk to HRVs and study personnel associated with firing live ammunition. It is necessary to use custom-loaded blank cartridges to dictate that the cartridge load meets the desired impulsive noise characteristics for the study and maintains tight tolerances in sound levels generated by the blank cartridges. The currently planned cartridge size for this study is a .36 Nosler (see Figure 6). Blank cartridges are shorter than live ammunition since there is not a projectile (Figure 4), a feature that will be exploited in the design of the BDA to mitigate risk of injury or misuse. This cartridge is favored because it is obscure and has no known use in the military. It also has a large propellant capacity, which will permit custom loads to produce a wide variety of impulse sound energy levels.



Figure 4. Example of differences between empty, blank and live 5.56 mm cartridges. An empty cartridge is furthest to the left. The blank cartridge is the second from left and the remaining five represent cartridges containing projectiles.

Note the shorter overall length relative to the cartridges containing projectiles. Image taken from <https://www.northropgrumman.com/Capabilities/5-56mmAmmunition/Pages/default.aspx>. Accessed 21 November, 2019.

Method of Exposure Delivery: Blank Discharge Apparatus

Impulses will be produced using a custom BDA. The BDA will not be designed to and may not readily be converted to expel a bullet and is not a destructive device, therefore it does not meet the criteria for classification as a firearm under 18 USC 921(a) (3) (see <https://www.atf.gov/firearms/firearms-guides-importation-verification-firearms-ammunition-gun-control-act-definitions>, last accessed 21 November, 2019). The discharge chamber(s) of the BDA generally follow the design principles for a universal receiver collar and test barrel, as described in ANSI-SAMMI Z299.4-2015 (p. 225-229). Briefly, a test barrel consists of a hardened metal cylinder designed to receive a cartridge of a known type (e.g., 5.56 mm x 45 mm

NATO) and sustain the forces generated during discharge of that cartridge (Figure 5 and Figure 6). The test barrel is housed within a universal receiver that has an outer diameter slightly less than 2 inches (50.75 mm). Each test barrel assembly is designed to have an outer diameter of 1 inch.

As noted, blank cartridges require less length than live ammunition, which contains a bullet. The test barrel assemblies used will be customized to prevent the insertion of live ammunition via a slight reduction of the diameter beyond the furthest extent of the blank cartridge.

The BDA consists of a large (approx. 1.8 meter [m] diameter) rotating steel disc with 72 equally-spaced universal receiver collars near the outer edge of the disc (Figure 7 and Figure 8). Prior to discharge of the blank discharge, the BDA disc will rotate and align with the selected universal receiver collar. Blank cartridges will be discharged using a custom-designed firing pin mechanism. The BDA will be mounted on an elevated platform with an ejecta gap leading to inflammable ballistic rubber blocks and exhaust fan inlets beneath the platform to receive combustion products.

The structural integrity of the test barrels and universal receiver collar assemblies will be verified using procedures similar to the procedures used with firearms. These tests involve the use of “proof” cartridges, which contain larger propellant charges and produce chamber pressures well in excess of the expected service pressure for the firearm. For example, the .36 Nosler cartridge produces a chamber pressure of approximately 65,000 pounds per square inch (PSI), and proofing cartridges for the .36 Nosler chamber produces approximately 93,000 PSI, which means that the chambers are proof-tested at approximately 1.4 times the expected pressures used in service. The pressures developed in a blank cartridge are lower than those for live ammunition because the cartridge and barrel are not occluded.

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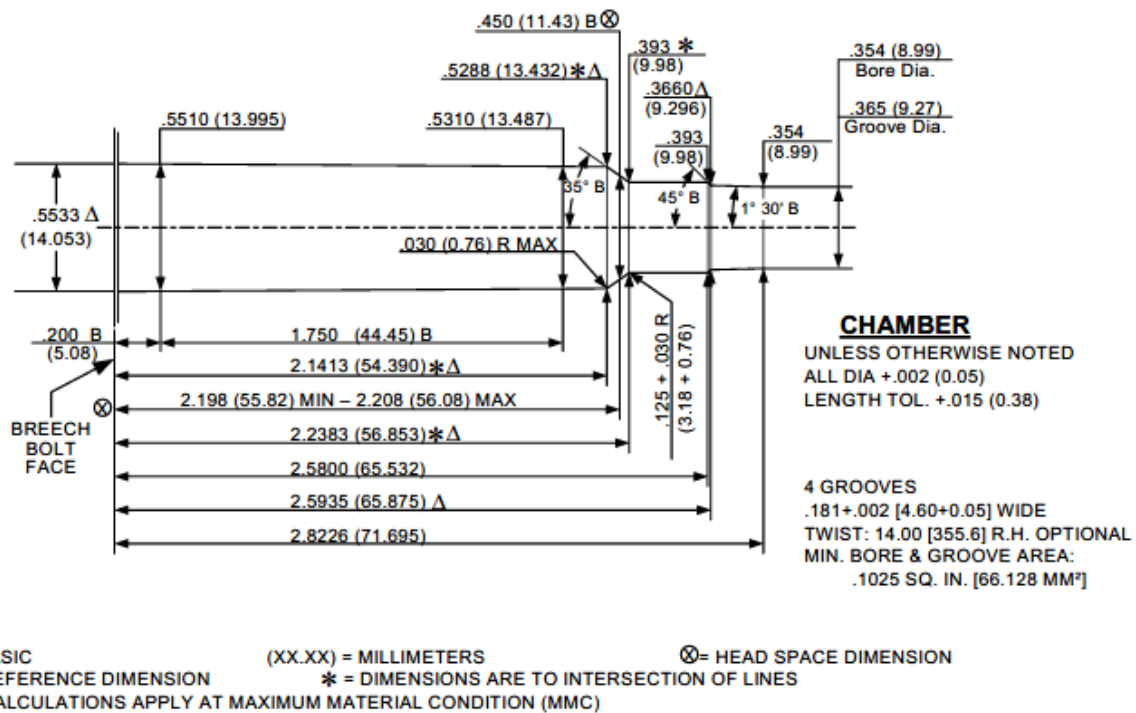


Figure 5. Test barrel interior dimensions for the .36 Nosler (live ammunition) cartridge.

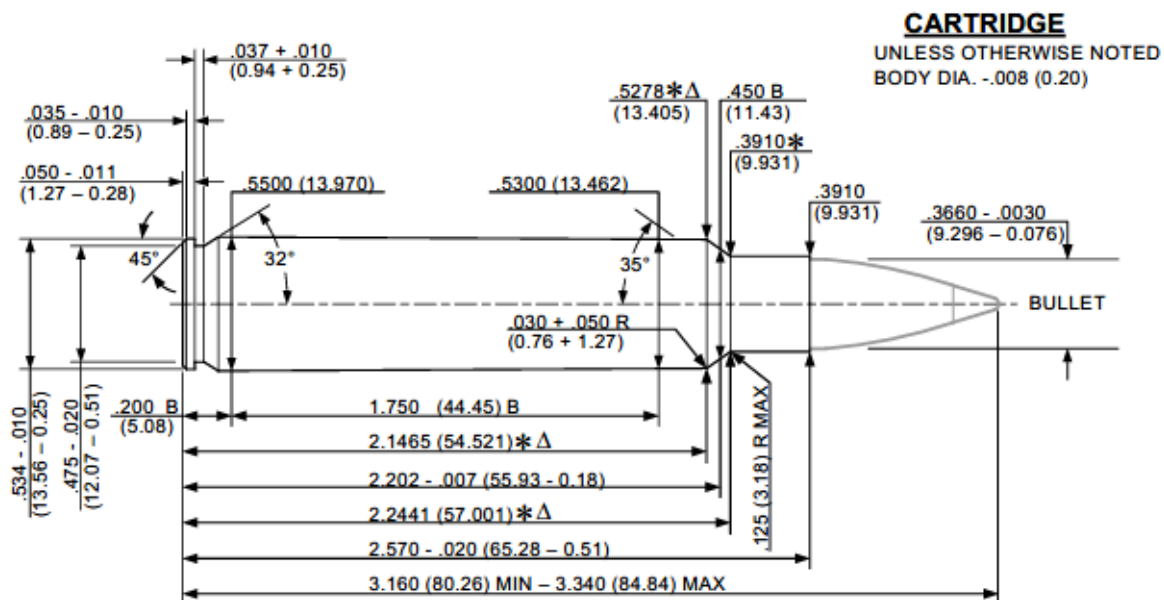


Figure 6. Cartridge (live ammunition) dimensions for the .36 Nosler. Note that the bullet extends approximately 15 mm beyond the cartridge case.

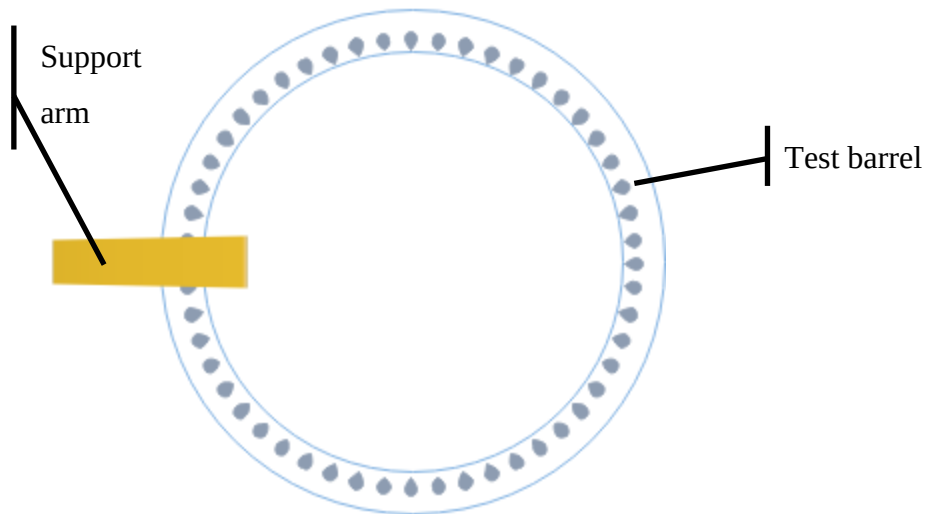


Figure 7. Rough line schematic of the BDA, top view (not to scale). The blue outer circle represents the extent of an approximate 1.8 m diameter disk constructed from sheet metal. Gray filled sections represent individual universal receiver collars.

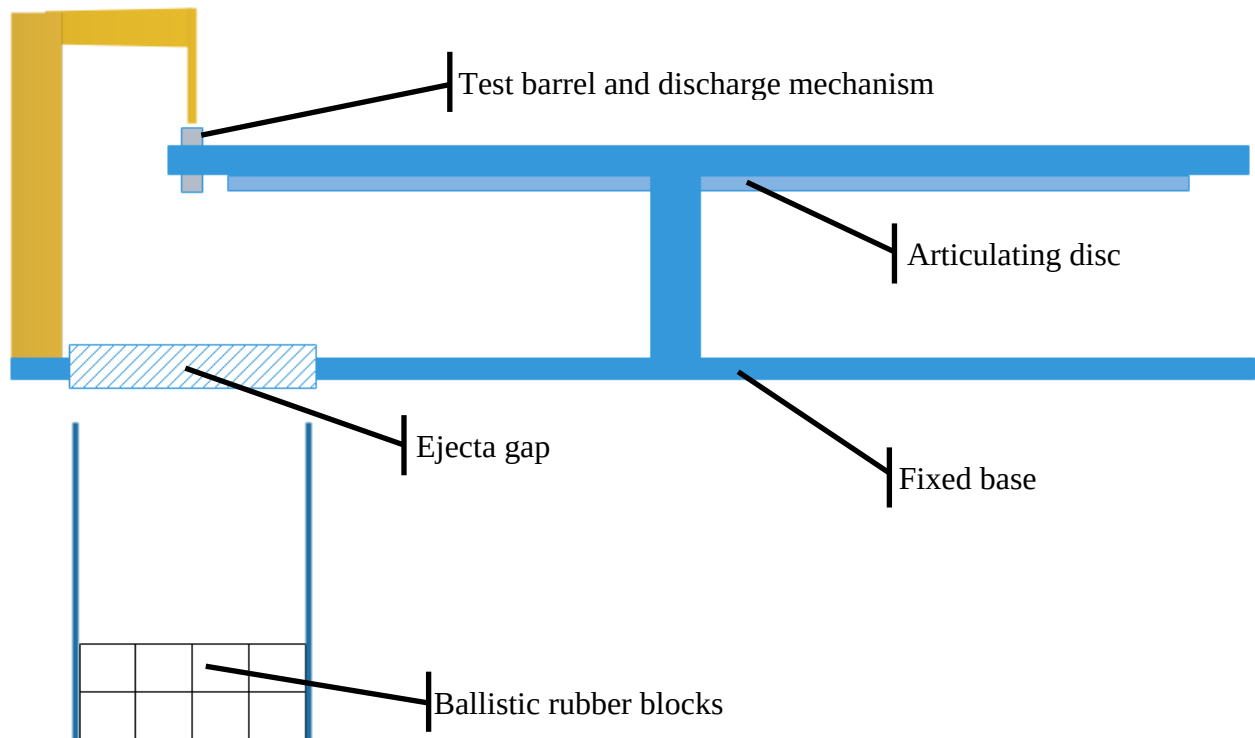


Figure 8. Rough line schematic of the BDA, side view (not to scale). The blue upper rectangle the approximate 1.8 m diameter disk constructed from sheet metal. Gray filled rectangle represents one universal receiver collar (full set not shown).

Study Population

Source and Number of Human Research Volunteers (HRV)

This study is designed to accommodate a total of 7 groups consisting of 64 HRVs (total $N = 448$), and each group will be presented only one stimulus level and class. Although the precise levels and ANOR values across candidate DRCs cannot be determined until the field site is prepared, we anticipate that these 7 groups can support DRC recommendations for at least two stimulus classes (i.e., quasi-free field and reverberant), including a control task cohort. The identification of an unsafe combination of type, level, and number of exposures (i.e., an exposure cell) is sufficient to generate a recommendation and will therefore close that stimulus class to additional testing with HRVs. The two mandatory stimulus classes for this project are quasi-free field and reverberant settings because the quasi-free field stimulus class best represents firing range conditions and because the long envelope durations and complex waveform fine structure could uncover differences between DRCs that rely on integrated energy (e.g., LAeq8, LIAeq8) and those that rely on complex mathematical models (e.g., ICE, AHAH). Closure of one or more stimulus classes due to the identification of unsafe exposures will permit the addition of more stimulus classes, listed in Section 4.

It is expected that the HRVs will be drawn from Service Members who just recently completed IET. However, locations(s) from which to recruit and enroll HRVs will be determined pending approvals from unit command/leadership, personnel, and incidental changes that may occur before the beginning of the project period.

HRV Selection Criteria

Inclusion criteria.

Criteria for eligibility to participate will be described to potential volunteers before they are asked to provide voluntary informed consent to participate (VIC). This permits potential volunteers who know they do not meet the inclusion criteria to decline participation without stating the reason for the decision, thus protecting confidentiality. No data will be collected about potential volunteers except the number of potential volunteers who attended an informed consent appointment and did not meet inclusion criteria or decided not to provide informed consent to participate. Potential volunteers will be selected without respect to sizes and shapes of heads, pinnae, or ear canals.

It is anticipated that potential HRVs will be recent IET graduates. The process of enlisting and qualifying for IET requires the full disclosure of medical history. This level of review is beyond the scope of the current study. However, knowledge of the medical standards and disqualifying conditions offers a baseline hearing health history to build upon with the study inclusion and exclusion criteria. The subsections of document Department of Defense Instruction (DoDI) 6130.03 Medical Standards for Appointment, Enlistment, and Induction into the Military (Department of Defense, 2018) relevant to the current study are in Table 2. There may be cases where a medical waiver is granted, however, Service Members who have been granted a medical waiver are not eligible to participate in the study.

Table 2. Relevant subsections of DoDI 6130.03 Medical Standards for Appointment, Enlistment, and Induction into the Military Disqualifying Conditions Section Rendering a Potential Service Member Ineligible to Enlist in IET without a Medical Waiver

5.5 EARS.

- a. Current defect that would require either recurrent evaluation or treatment or that may reasonably be expected to prevent or interfere with the proper wearing or use of military equipment (including hearing protection) to include atresia of the external ear or severe microtia, congenital or acquired stenosis, chronic otitis externa, or severe external ear deformity.*
- b. Any history of Ménière's Syndrome or other chronic diseases of the vestibular system.*
- c. History of any surgically implanted hearing device.*
- d. History of cholesteatoma.*
- e. History of any inner or middle ear surgery.*
- f. Current perforation of the tympanic membrane or history of surgery to correct perforation during the preceding 180 days.*
- g. Chronic Eustachian tube dysfunction within the last 3 years as evidenced by retracted tympanic membrane, or recurrent otitis media, or the need for pressure-equalization tube.*

5.6. HEARING.

- a. Audiometric hearing levels are measured by audiometers calibrated to the standards in American National Standards Institute S3.6-2010 and will be used to test the hearing of all applicants.*
- b. Current hearing threshold level in either ear that exceeds:*
 - (1) Pure tone at 500, 1000, and 2000 cycles per second for each ear of more than 25 decibels (dB) on the average with any individual level greater than 30 dB at those frequencies.*
 - (2) Pure tone level more than 35 dB at 3000 cycles per second or 45 dB at 4000 cycles per second for each ear.*
 - (3) There is no standard for 6000 cycles per second.*
- c. History of using hearing aids*
- k. Pregnancy through 6 months after the completion of the pregnancy.*
- b. Current or medically-managed hypertension. Hypertension is defined as systolic pressure greater than 140 millimeters of mercury (mmHg) or diastolic pressure greater than 90 mmHg confirmed by manual blood pressure cuff averaged over two or more properly measured, seated, blood pressure readings on separate days within a 5-day period (isolated, single-day blood pressure elevation is not disqualifying unless confirmed on 2 separate days within a 5-day period).*
- o. History of Neurofibromatosis I (Von Recklinghausen's Disease), Neurofibromatosis II*
- y. History of any medical condition severe enough to warrant use of systemic steroids for greater than 2 months, or any use of other systemic immunosuppressant medications.*
- j. History of industrial solvent or other chemical intoxication with sequelae.*

Diabetic disorders, including:

- (1) History of diabetes mellitus.*
- (2) History of unresolved pre-diabetes mellitus (as defined by the American Diabetes Association) within the last 2 years.*

e. History of diabetes insipidus.

g. History of moderate or severe brain injury if associated with:

- (1) Post-traumatic seizure(s) occurring more than 30 minutes after injury;*
- (2) Persistent motor, sensory, vestibular, visual, or any other focal neurological deficit;*
- (3) Persistent impairment of cognitive function;*
- (4) Persistent alteration of personality or behavior;*
- (5) Cerebral traumatic findings, including but not limited to epidural, subdural, subarachnoid, or intracerebral hematoma on neurological imaging;*
- (6) Associated abscess or meningitis;*
- (7) Cerebrospinal fluid rhinorrhea or otorrhea persisting more than 7 days;*
- (8) Penetrating head trauma to include radiographic evidence of retained foreign body or bony fragments secondary to the trauma, or operative procedure in the brain; or*
- (9) Any skull fracture.*

h. History of mild brain injury if:

- (1) The injury occurred within the past month;*
- (2) Neurological evaluation shows residual symptoms, dysfunction or activity limitations, or complications;*
- (3) Two episodes of mild brain injury occurred with or without loss of consciousness within the last 12 months; or*
- (4) Three or more episodes of mild brain injury.*

i. History of persistent post-concussive symptoms that interfere with normal activities or have duration of more than 1 month. Symptoms include but are not limited to headache, vomiting, disorientation, spatial disequilibrium, impaired memory, poor mental concentration, shortened attention span, dizziness, or altered sleep patterns.

m. Any atraumatic seizure occurring after the 6th birthday, unless the applicant has been free of seizures for a period of 5 years while taking no medication for seizure control, and has a normal sleep-deprived electroencephalogram and normal neurology evaluation while taking no medications for seizure control.

Note. Medical conditions listed in this table could potentially impact the outcomes of the current study.

Inclusion criteria:

- Ages 18 to 29 years old at the time of the informed consent visit.
- Willingness to participate in a study requiring full-time temporary duty (TDY) to a study site for 16 days, and up to 20 days.
- Successful completion of IET.
- No issuance of medical waiver or assignment limitation during your time in the military.
- Must have qualified or re-qualified with a military weapon within the past 24 months.
- Must be eligible to handle an unloaded M4 carbine.
- No history of medications that affected hearing (ototoxic medications).
- No history of antibiotics that were injected into the bloodstream ([intravenous] IV antibiotics).
- No history of surgery of the ear or bone surrounding the ear (temporal bone or mastoid).
- No history of skin allergies, sensitivity to cosmetics, lotions, or alcohol-based hand sanitizers.

- Not currently pregnant.
- No current or history of bothersome tinnitus.
- No current prescription medication use (except birth control).
- No current participation in other research studies.

Exclusion criteria.

Exclusion criteria include those factors that are unlikely to be known prior to testing conducted during the enrollment appointment. We shall provide a non-technical description of the exclusion criteria during the process of explaining the study (prior to obtaining documentation of informed consent) and will explain when tests of these criteria will be conducted. The exclusion criteria are listed below.

- Features or physical disabilities that interfere with the proper fitting of the study. Measurement equipment or those that might arise from birth defects, ear surgery, or personal adornments.
- Ear canal abnormalities, such as exostoses (bony growths in the ear canal), as determined via otoscopic examination.
- Ear canal size and shape inappropriate for use with the available ear canal probe tips.
- Excessive cerumen (ear wax), irritation, tympanic membrane perforation, or infection (as determined by otoscopic examination and/or tympanometry) - Any of these conditions will result in either dismissal from the study or postponement of further procedures until the condition resolves - as the subject chooses.
- Hearing thresholds at 0.5, 1, 2, 3, and 4 kHz not more than 20 dB hearing level (HL), and hearing threshold at 6 and 8 kHz not more than 25 dB HL.
- Thresholds differing by more than 20 dB across ears at any one frequency.
- Abnormal middle ear function as determined using conventional tympanometry, clinical wideband immittance at ambient pressure and wideband tympanometry.
- Bothersome tinnitus prior to IET, or current, determined via self-report using the Tinnitus Hearing Survey.
- Self-report of pregnancy.
- Severe or very severe headaches, as determined via self-report.

Enrollment Procedures

Recruitment process

HRVs will be recruited from the population of early-career U.S. Service Members. With leadership/command approval, study personnel will make a brief (10 minute or less) presentation to an assembly of 75 or more Service Members. This presentation includes basic information about the study purpose, time commitment, risks, voluntary participation, confidentiality, and an invitation to request further information by telephone, text message, or email to a military email address used only for this study. This presentation will be observed by an ombudsperson responsible for overseeing the conduct of the recruitment process. The telephone number will route to a government-owned telephone and the email will be accessible only on a government-owned computer. No contact information will be transferred from this telephone or computer to

devices that are not owned by the U.S. government. Records will track on a weekly basis the numbers of potential volunteers lost to follow-up after initial contact, exiting after describing the inclusion criteria, or choosing informed refusal after the informed consent document was presented.

Voluntary informed consent procedure

Potential volunteers (i.e., Service Members who contact study personnel by telephone, text, or email) will be scheduled for a 1-hour private information session. The research staff will list all inclusion criteria with a brief description of each and then ask if the potential volunteer meets all the criteria. Only a general “yes” or “no” response will be requested so the research staff will not know which inclusion criteria were not met. If the potential volunteer indicates they do not meet all inclusion criteria, they will be thanked for their time and the session will end. No personally identifiable information (PII) or other information will be collected from potential volunteers who are dismissed prior to providing VIC. If the potential volunteer indicates that they meet all inclusion criteria, the research staff will describe the major elements of the informed consent document (e.g., purpose of the study, what will happen during the research, duration of involvement, possible risks and discomforts, possible benefits, what happens in the event of an injury, privacy and confidentiality, informed refusal, dismissal, withdrawal without penalty or prejudice), inviting questions throughout the description. Potential volunteers will be asked to complete a teach-back (Kripalani, Bengtzen, Henderson, & Jacobson, 2008) process to confirm their understanding of the purpose, risks, and potential consequences of volunteering for the study. HRVs will be classified as having the capacity to decide whether to participate if they can describe the study purpose and selected procedures, risks, potential benefits, alternatives, withdrawal process, and time commitment for those completing the research. Potential volunteers will be permitted to sign the informed consent document. Once the informed consent document is signed, the potential volunteer has acceded to HRV status. If potential volunteer chooses not to sign, they will be thanked for their interest and time and not enter the study. The informational visit will be observed by an ombudsperson responsible for overseeing the conduct of the recruitment process.

HRVs will be invited to complete the eligibility determination visit only after successful completion of the teach-back process and providing VIC.

Study Procedure

Study Setting

The study is designed to be conducted at three kinds of sites (*Figure 9*). A recruitment site (green) is a mobile site that will allow for recruitment and study informed consent activities to occur at locations convenient to Service Members. All HRVs selected to participate will be transported to the study site, which is divided into the exam site (pink) and field site (blue). The field site will be housed on military property. The exam site will be nearby, and may be on either military or non-military property (e.g., an office building in a city nearby). All procedures occurring during recruitment, VIC, eligibility determination visit, exam site, and pre- and post-dose administration series pose no more than minimal risk to HRVs. The dose administration

series (blue) is the only portion of the study involving exposure to noise levels that would be considered greater than minimal risk.

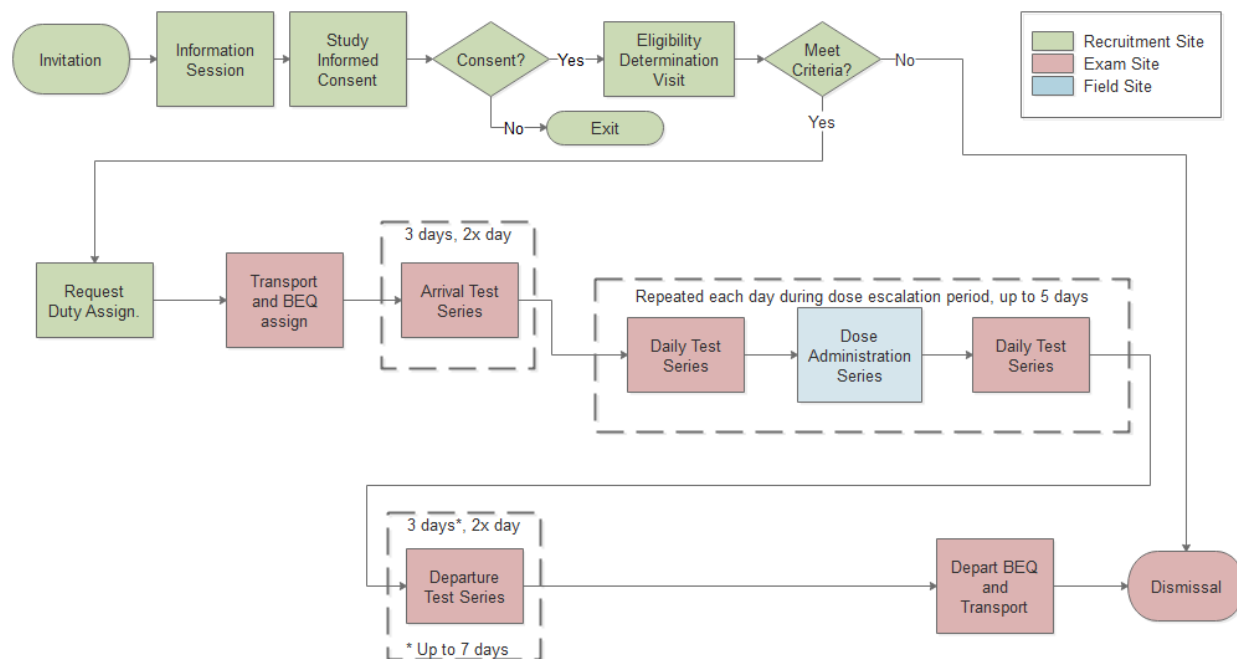


Figure 9. Overall study flowchart.

During participation in the study, HRVs will have access to general military facilities when not engaged in study procedures at the exam and field site. The general military facilities include living quarters (Bachelors Enlisted Quarters or better), dining facilities, commissary, military health facilities, and additional Morale, Welfare, and Recreation resources.

HRV time commitment.

The total time commitment for HRVs ranges between 1 hour and 88 hours. The sample calendar below shows the expected study timeline and daily time commitment (Figure 10). The group presentation, VIC and eligibility determination visit may not occur on consecutive days, but the time commitment remains unchanged. HRVs will be instructed to expect engagement in study activities approximately 7.5 hours per day for 11 days (arrival, dose exposure, and departure test series), not including weekends. For HRVs completing all study procedures, the total time commitment of up to 16 days away from routine duties could be possible, depending on travel, housing, weather delays, and other logistics. HRVs will be provided with lodging, food, and time to meet daily physical training. Eight HRVs will complete this schedule at a time, with subgroups of 4 in staggered testing throughout the day. If an HRV withdraws from the dose administration series early (but chooses to continue with the exam portions of the protocol), or if a dose exposure level closes early, the remaining dose exposure series days will be converted to additional days in the departure test series. The extended departure test series is important because, in the event of an early stop to the dose administration, additional time will be available to monitor the affected HRVs return to baseline and/or identify late-appearing effects.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
July 26	27	28	29	30	31	August 1
2	3 Group Presentation 10 minutes	4 Information Session 1 hour, plus 20 minutes scheduling time.	5 Eligibility Determination Visit 1.5 hours	6	7	8
9	10	11	12 Arrive at Study Site Inprocessing and minimal paperwork 1 hour	13 Arrival Test Series Day 1 7.5 hours	14 Arrival Test Series Day 2 7.5 hours	15 Arrival Test Series Day 3 7.5 hours
16	17 Dose Exposure Series Day 1 7.5 hours	18 Dose Exposure Series Day 2 7.5 hours	19 Dose Exposure Series Day 3 7.5 hours	20 Dose Exposure Series Day 4 7.5 hours	21 Dose Exposure Series Day 5 7.5 hours	22 Hearing Sensitivity Testing if needed 30 minutes
23	24 Departure Test Series Day 1 7.5 hours	25 Departure Test Series Day 2 7.5 hours	26 Departure Test Series Day 3 7.5 hours	27 Depart from Study Site 1 hour	28	29
30	31	September 1	2	3	4	5

Figure 10. Example volunteer schedule.

Personnel training and oversight.

Data collection and analysis will be monitored on multiple levels by several members of the research team. Prior to data collection, study technicians will undergo training to become certified occupational hearing conservationists (OHCs) and will be cross-trained on all research protocols. These personnel will be trained to conduct testing and identify atypical results. Data discrepancies and abnormalities will be logged into electronic files as metadata and brought to the attention of key personnel (e.g., site managers and key personnel), who will also monitor data collection procedures continually. Well-defined research protocols and summary sheets (“job aids”) will be developed for all test procedures, and daily oversight will be provided by key personnel (e.g., audiologist, engineer). Key personnel will have access to encrypted virtual private network (VPN) connections to the exam and field sites in support of oversight and troubleshooting. Protocol execution will be governed by custom software that automates test order, recorded/printed instructions, and necessary technician prompts. Software will also automatically calculate summaries and notify technicians of key events (e.g., suspected criterion TTS, substantial deviations from typical results). To minimize protocol deviations and to ensure uniformity, identical scripts will be used across all test locations where a given protocol is executed. Data returned from study procedures will be subjected to multiple levels of review by study personnel to ensure quality and provide early warning of problems.

A daily calibration procedure will be conducted for all equipment at the start and end of each day of testing. Customized computer applications and written protocols will be used to systematize the process, ensure reliable execution, and flag results indicating hardware

malfunction. Calibration records will be monitored regularly by key personnel for subtle changes indicating possible hardware malfunction. Personnel will comply with the current military and U.S. Centers for Disease Control and Prevention guidelines for cleaning and disinfecting all common areas, test spaces, and materials. Single use materials will be utilized when available.

Eligibility determination visit.

The eligibility determination visit procedures are completed to determine eligibility to participate in the study, and the procedure is expected to take 1.5 hours. The eligibility determination visit procedures (Figure 11) will begin by confirming the HRV's identification and assigning an anonymous unique Human Research Volunteer ID (HRVID). The HRVID will be coded into a linear barcode (Figure 12) on a durable wristband that the HRV will be asked to wear upon arrival at the study site and continue wearing for the duration of their voluntary participation in the study. The linear bar code HRVID will be scanned prior to each test procedure and saved to each data file, linking HRV data to the correct HRVID to minimize errors linking de-identified data to HRVID and minimizing the use of PII in the study procedures. The HRVID will not be printed alphanumerically on the wristband as a safeguard against loss of confidentiality or potential linking of HRVID to data or PII.

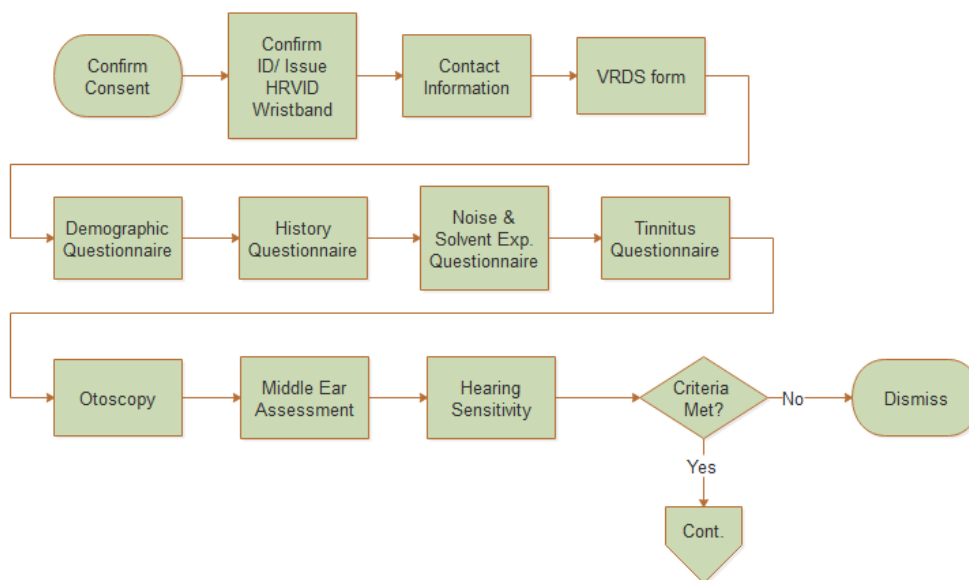


Figure 11. Eligibility determination visit series, completed following successful teach-back process and VIC.



Figure 12. The durable wristband worn by each HRV during their participation in the study will contain a linear barcode similar to this example. No other information, including PII or HRVID, will be labeled on the wristband.

Arrival and departure series.

The arrival test series will be completed prior to beginning the dose administration series. This is a series of baseline tests that will be conducted twice daily for three days. HRVs will participate in the arrival test series approximately 7.5 hours per day. The arrival test series is intended to obtain baseline results for measures obtained throughout the project, measure HRV characteristics that might influence individual susceptibility (e.g., acoustic transfer function of the test ear, magnitude of otoacoustic emission (OAE) suppression under contralateral stimulation, and the magnitude and habituation of the startle response to a tactile air puff elicitor), measure the attenuation of the hearing protector used in the non-test ear, and monitor for unexpected adverse outcomes (e.g., reductions in extended high-frequency hearing sensitivity, degradation of working memory). The departure series occurs on the three days following the last exposure period, and includes the same series of tests as the arrival series. The aim of the departure series is to monitor for subtle changes that may have occurred during the exposure period, and to verify that hearing levels have returned to baseline levels in cases where HRVs have shown TTS.

Upon arrival at the study site, HRV identity will be confirmed. HRVs will be asked whether they continue to consent to voluntary participation in the study, and will complete the Arrival Questionnaire (Appendix 1) to confirm whether they still meet the inclusion criteria (Section 6.2) to participate in the study. The following day, HRVs will be transported to the exam site to begin the arrival test series (Figure 13). After explaining the components of the arrival test series, HRVs will be asked to provide continued VIC or informed refusal/withdrawal of consent. For HRVs who discontinue participation, they will be asked to choose whether to discontinue from the study entirely, or discontinue participation only in the exposure period. HRVs choosing to discontinue only the exposure period will begin the departure series the following day. If the HRV previously began the dose escalation process, the purpose of the departure series will be to monitor recovery from any TTS and detect any late-appearing changes.

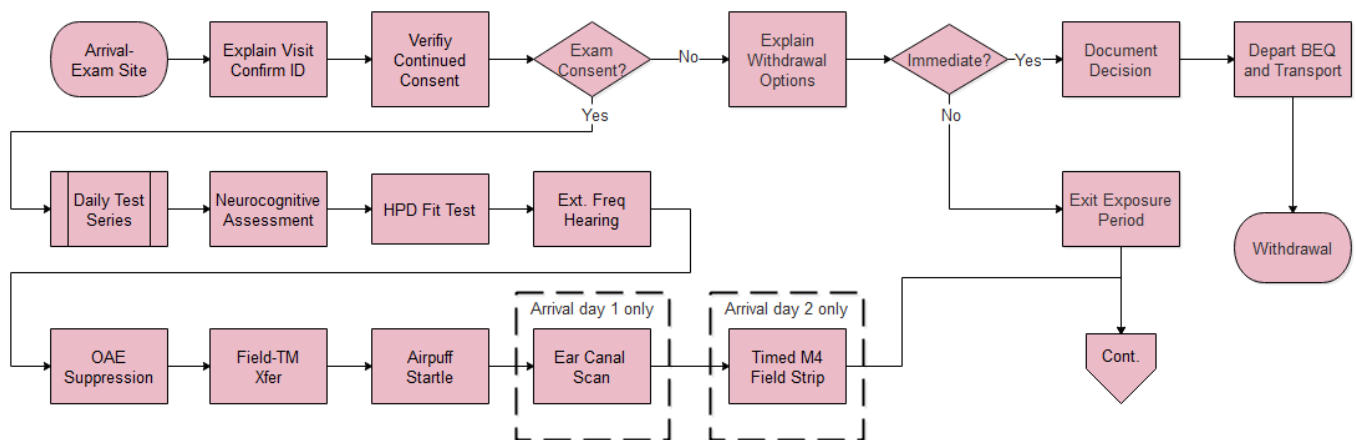


Figure 13. Arrival and departure series, completed twice a day for three days before and after the dose escalation exposure series.

Upon completion of the dose administration series, HRVs will complete the departure series tests twice daily for three days plus any additional days the dose exposure series was not

completed. The departure series parallels the arrival test series with the exception of the ear canal scan, which is only completed on day one of the arrival series. All tests are completed during the departure test series to compare to the arrival series baseline results. The departure test series also provides the additional testing to monitor cases of criterion TTS, and to examine the influence of the dose series on non-threshold hearing, tinnitus, balance, and neurocognitive status. Upon completion of the departure series, the HRV will have completed all study procedures and be dismissed to return to their regular unit.

Daily test series.

The daily test series procedures will be completed during the arrival and departure series (Figure 14, expected 2 times daily for 6 days, 12 total) and before and after each dose administration series (Figure 15, expected 2 times daily for up to 5 days, 10 total). All HRVs in a subgroup (n=4) will complete the daily test series concurrently, whether embedded in the arrival and departure series or surrounding the dose administration. This set of procedures is designed to monitor for: recovery from possible TTS; secondary effects of exposure (e.g., changes in otoacoustic emissions, reductions in tinnitus loudness, changes in potential indicators of possible synaptopathy, changes in balance function); identify incidental changes in auditory function due to coincidental conditions (e.g., upper respiratory infection). During the arrival and departure series, the daily test series is designed to provide a baseline and to monitor recovery to baseline levels.

In addition, the daily test series provides additional opportunities for HRVs to declare their decision to either continue participation or withdraw from the study. Upon arrival, staff will provide an overview of the testing to be completed, and HRVs will be asked to verify that they have decided either to continue the study or withdraw. Those who withdraw from the study will choose whether to withdraw immediately (logistical exit plans will begin immediately), or withdraw from the dose administration only (departure series testing will begin), as described above. HRVs choosing to continue to participate will be eligible to complete the planned study procedures for that day. Order of procedures will vary based on whether an HRV begins in room A, B, C, or D (order variation shown in Figure 14). The varying procedural order is included in the design for practical reasons and is not expected to influence study results.

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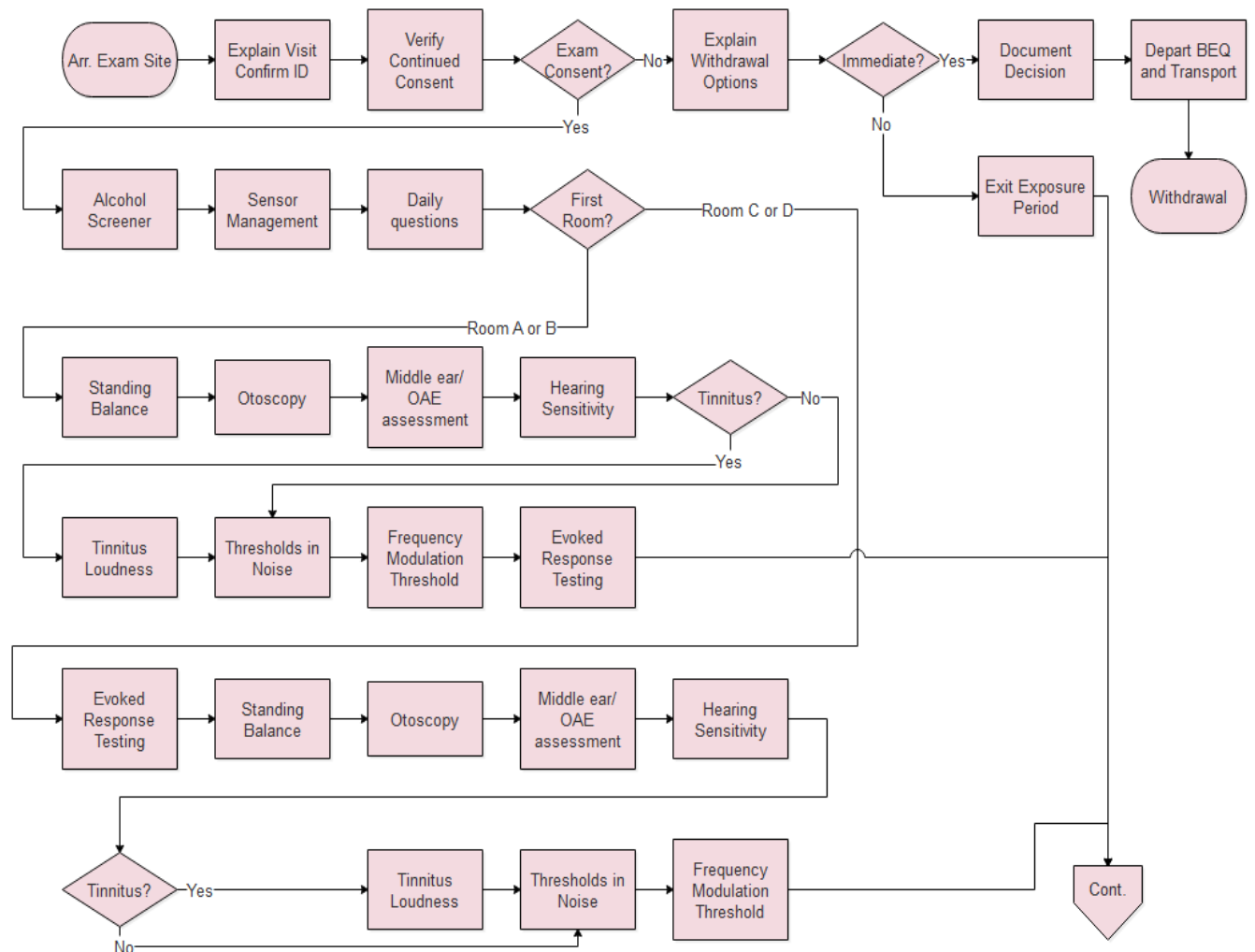


Figure 14. Daily Test Series, embedded within the arrival and departure series, and before and after every dose administration series.

Dose administration series.

If an HRV elects to withdraw from the study during the dose administration series, study personnel will inform the HRV that he/she may choose to withdraw immediately, or he/she may choose to withdraw from the dose administration series only. If the HRV chooses immediate withdrawal, the decision will be documented, the HRV will be released from the study, and assignment to their next duty will be facilitated without prejudice. If the HRV chooses to withdraw from the dose administration series only, they will exit the exposure period of the protocol and begin the departure series.

Following the three days of arrival test series, HRVs who choose to continue will take part in up to five dose administration series (Figure 15). The dose administration series include the level and number of exposures that are necessary to affirm or rule out the DRC(s) in question. The pre- and post-test series are completed to monitor the immediate direct effects of each dose. The entire dose administration series occurs at the field site. The staging area will be an indoor mobile office space next to the exposure platforms. The pre- and post- test station is

directly below the dose exposure platform (i.e., inside the shipping container used as the platform). The dose exposure space will vary with the stimulus class. For the quasi-free field stimulus class, HRVs will be seated on a walkway and seating area positioned atop a shipping container. In the reverberant stimulus class, HRVs will be seated inside an acoustically-modified shipping container stacked on top of the base container.

After completion of the pre-exposure daily test series, HRVs will be transported to the field site. HRVs will be paired with a single hearing technician and an explanation of the field site visit and confirmation of continued consent to participate in the dose series will occur upon arrival. HRVs choosing to withdraw from the exposure series only will begin the departure test series. HRVs consenting to continue the exposure will continue with the series.

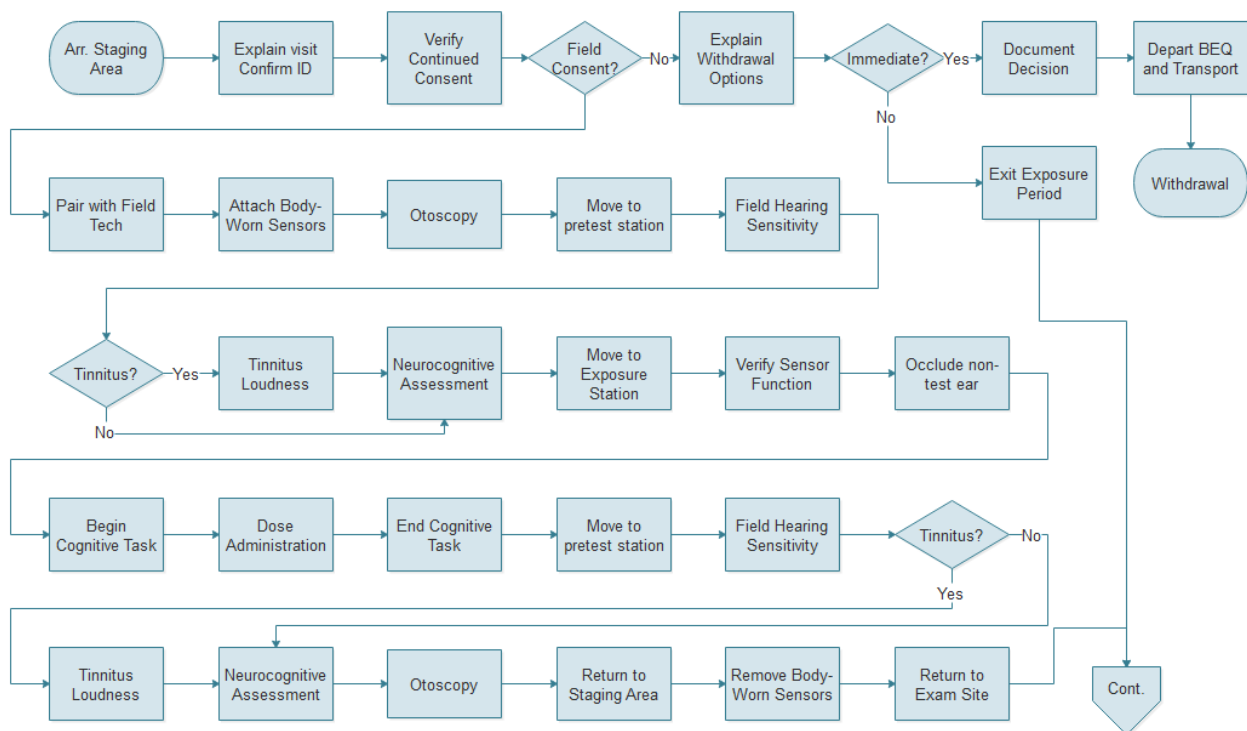


Figure 15. Dose administration series, completed up to 5 times. The dose administration series is the only portion of the entire study that is considered greater than minimal risk.

Study Procedure Site

The proposed study involves work at different sites. A mobile site will be established for recruitment, voluntary informed consent, and the Eligibility Determination Visit and another installation will serve as the exam and field site with suitable year-round weather to support regular outdoor exposures with minimal likely inclement weather interruptions, which can compromise study results (Hancock, Ross, & Szalma, 2007) and damage sensitive instruments. The recruitment and VIC activities require no special environments beyond a quiet room.

The exam site requires an environment with multiple quiet rooms (~1500 square feet) to support simultaneous protocol completion with each subgroup of four HRVs under noise-

attenuating earphones, facilities to support electrophysiologic testing, plus other amenities common to a health clinic (e.g., temperature and humidity control, running water).

The field site requires a large (83 x 83 m) remote area that is nearly level and preferably features electrical service. A set of 12 40-foot (12.9 x 2.44 x 2.59 m) metal shipping/storage containers will be arranged at the field site so that the ends of 8 containers each form an octagon. Alternating containers along the octagon will be stacked two units high. The 4 unstacked containers will be outfitted with a platform and handrails to support one seated HRV, study personnel, and all necessary hardware for quasi-free field conditions (Figure 16). The interiors of the 4 stacked containers will be outfitted similarly to support reverberant stimulus conditions (Figure 17). A blank discharge apparatus (BDA) will be located in the center of the octagon so that, when discharged, the impulse will arrive at the HRV locations at approximately the same time and magnitude. The 8 base trailers will contain the signal cables for the HRV locations and sound-treatment to permit pre- and post-exposure assessment using attenuating earphones. A mobile office, which is essentially a shipping container with tamper-resistant doors and bars over the windows and HVAC, will house the HRV preparation/staging area, exposure control station, seating, and equipment storage space.

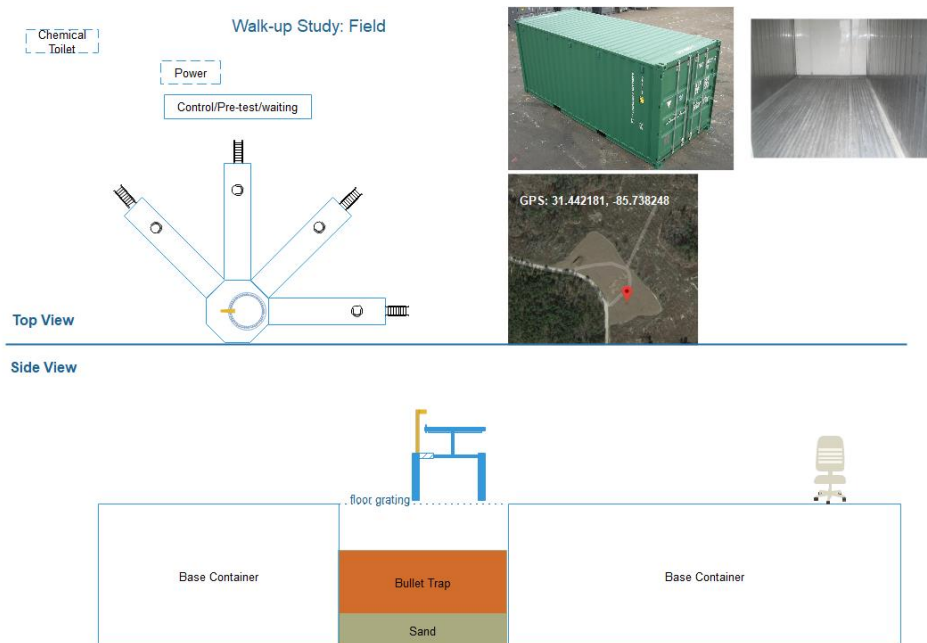


Figure 16. Line schematic of top and side view of test environment for field setting. The test environment is constructed from commercial shipping/storage containers arranged along the segments of an octagon. The BDA will be located with the discharge site at the center of the octagon. Measurement locations, which are depicted as chairs in both views, will be located on the top surfaces of the base containers. The container array will support measurements of four participants simultaneously. Stairs, flat walking surfaces, and hand rails installed on the top surfaces and railings will be used to demarcate and prevent falls. HRVs will be seated in chairs during exposure intervals. Blank cartridges will be discharged from the center of the octagon formed by the container ends. The blank firing apparatus will be operated from the secure mobile

office. Pre- and post-exposure testing will be conducted inside the container directly beneath each exposure location.

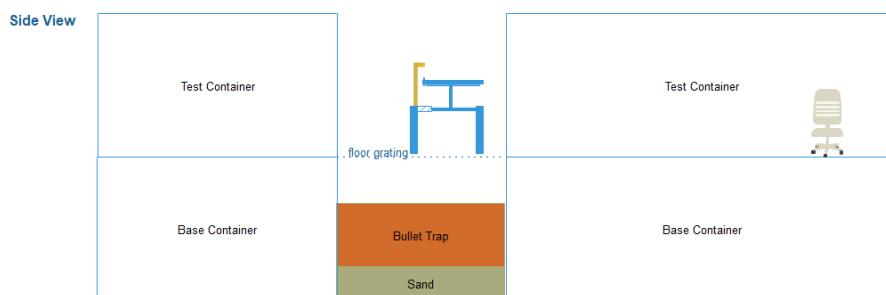


Figure 17. Line schematic of the side view of test environment for reverberant setting. Details are similar to the quasi-free field setting, except that measurements are located inside containers having open doors at the end closest to the BDA.

Test Procedure Details

A large number of test procedures will be performed across the eligibility determination visit, the arrival and departure test series, the daily test series and the dose administration series and many test procedures will be repeated throughout study participation. Details of the study test procedures as well as where those procedures fall within the study components are described below.

Eligibility determination questionnaires (Eligibility visit).

During the eligibility determination visit, the HRV will be asked to provide basic contact information (name, phone number, email address) and complete Part B of the Volunteer Registry Data Sheet (VRDS USAMRDC 60-R) form. These two forms containing PII will only accessible to key personnel and will be stored separately from the remaining questionnaires and study data. The HRV will be asked to provide responses to demographic, history, noise and solvent exposures, tinnitus, and neurobehavioral questions written or electronic format (Appendices 2-5). Demographic questions will include two-digit military occupational specialty (MOS) career management field (CMF) code or equivalent for other DoD branches (e.g., 11 for Army Infantry Branch), sex/gender, current age in years, and educational attainment. The race/ethnicity question is used by the U.S. National Center for Health Statistics in the National Health and Nutrition Examination Survey (NHANES) to obtain 5 race/ethnicity groups (non-Hispanic Black, non-Hispanic White, Mexican American, Other Hispanic, Other Race – including Multi-Racial). History questions will include relevant medical items (e.g., history of ear infections, ear surgery, ototoxic medications, hearing trouble, balance problems, neurobehavioral symptoms). Noise and solvent questions, based on the LENS-Q (Bramhall, Konrad-Martin, McMillan, & Griest, 2017), ask questions about detailed history of military, occupation, and non-occupation exposures. Tinnitus questions are based on the Tinnitus and Hearing Survey (THS) (Henry et al., 2015). Neurological symptom questions were derived from the Neurobehavioral Symptom Inventory (NSI) (Caplan et al., 2010). Both the LENS-Q and the THS were developed with U.S.

Government support and are publicly available. All questionnaire forms used in this study are either publicly-available or were formatted by the investigators for use in this or prior studies.

Middle ear assessment (Eligibility visit, Daily test series).

Middle ear status will be assessed at each daily visit series using the Interacoustics Titan middle ear analyzer. This procedure includes conventional tympanometry (tympanometric pressure and admittance, equivalent ear canal volume, and tympanometric width), acoustic reflexes (only during arrival/departure test periods), wideband absorbance at ambient pressure, and wideband tympanometry. In addition, the Etymotic ER-10 series otoacoustic emission probe system will be used to obtain distortion product otoacoustic emissions (DPOAEs) results during the daily test series. During the middle ear assessment, a soft, rubber tip will be gently inserted into each ear canal to produce a hermetic seal. During the testing, HRVs will be asked to sit quietly with minimal movement while they hear some tones and clicks. Some of the tones will be loud, but brief. They will be told they may experience a change in pressure that feels similar to being in an airplane or elevator. These results will be used to determine eligibility into the study.

Otoscopy (Eligibility visit, Daily test series, Dose administration series).

A video otoscopic examination will be conducted, using a Welch-Allyn Digital Macroview video otoscope, to document the status of each ear canal and eardrum at the time of eligibility determination and alert the HRV to any issues that require attention (e.g., cerumen preventing a view of 60% of the tympanic membrane) before continuing at the exam site. During the study, otoscopy will be performed to confirm ear canal status and provide a reference image for comparison within and across days. Staff will not perform cerumen removal, and will recommend to HRVs that they could obtain this service from the local military treatment facility. Video recording will include only the pinna, outer ear, ear canal, and ear drum. Video recording will not include the HRV's face. HRVs will be asked to sit with head still while staff pulls gently back and up on each pinna while using the opposite hand to insert the speculum of the otoscope in the outer ear canal (Figure 18). The staff member will use a foot pedal to engage and stop the video recording.

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Figure 18. Research staff will pull the HRVs pinna up and back while inserting the otoscope speculum into the outer ear canal. Staff will be trained to brace the outer portion of the hand holding the otoscope on the HRVs face to prevent discomfort in the unlikely event of sudden HRV movement.

Hearing sensitivity (Eligibility visit, Daily test series, Dose administration series).

Hearing sensitivity evaluation, using a fixed-frequency Békésy (Békésy, 1947) procedure (NI Békésy Pro cDAQ hardware, VAcoustics Békésy Pro software, RadioEar DD450 circumaural earphones), will be used to confirm hearing sensitivity is within the limits for study participation. The DD450 circumaural earphones use soft padding that encircles the ear for increased comfort and isolation from ambient noise. Pure tone thresholds will be obtained from .5 to 8 kHz inclusive, and including interoctave frequencies 3 and 6 kHz.

Fixed-frequency Békésy audiometry involves testing one frequency at a time. The stimulus parameters used in this study follow Murphy, Byrne, Witt, and Duran (2005). Pulsed tones (250 ms, 50% duty cycle) at the selected stimulus frequency will be swept through intensities at a rate of 5 dB/s. The listener is instructed to press and hold a button the entire time the tone is heard. The button press causes the intensity progression to reverse and attenuate. When the listener no longer hears the tone and stops pressing the button, the tone reverses again and begins increasing in intensity. A total of 8 reversals are required to determine threshold, which is based only on the last 6 reversals. For naïve listeners, midpoints between successive reversals have been shown to have a within-trial standard deviation (SD) between 0.3 to 2.5 dB and a between-trial SD between 0.2 and 5 dB (Murphy et al., 2005). Threshold is typically determined within 30 seconds to one minute per frequency. Hearing sensitivity evaluations will be conducted during the eligibility determination visit, the daily test series, and pre- and post-dose administration series. HRVs will have completed Békésy tracing at least 246 times during eligibility determination and arrival visits, and the effects of learning the procedure are expected to reach asymptote prior to completing the arrival series. These results will inform HRV eligibility to participate and will be used as the primary study outcome (criterion TTS).

Ear canal scan (Arrival test series).

During the first day of the arrival test series, each HRVs ear canals will be scanned using the Lantos 3D scanner (Figure 19). A single-use membrane, made from biocompatible, medical-grade material, is attached to the tip of the Lantos Scanner. The tip is inserted into the ear canal within 4-5 mm of the eardrum (confirmed optically), where it inflates (expanding radially) and conforms to the 3-dimensional shape of the HRVs ear canal. The interior of the membrane is scanned and converted into a quantitative 3D model of the HRVs ear. These scans will be used to examine the characteristics of each HRVs ear, and characteristic features may be used as a covariate of changes in auditory performance. The 3D model of the right ear will be used to produce an earplug for use during the dose administration series. The procedures for producing the earplugs will follow the general procedures used by Stefanson and Ahroon (2019) with this device. The Original Prusa SL1 3D printer plus curing and washing machine bundle will be used to print the re-usable earplug using Class I (short term, frequently used during dental procedures) or Class II (long term, can be used to make dentures) biocompatible resin. The custom earplug attenuation will be measured via HPD Fit Testing, described below.



Figure 19. Lantos 3D scanner and single use Lantos Membrane, for use in ear canal 3D scanning.

Timed M4 carbine disassembly, assembly, and performance check (Arrival test series).

During day 2 of the arrival test series, HRVs will perform a timed task as an indirect measure of firearm skill and comfort level. This information will be used as a representation of general weapon familiarity and as a covariate of changes in auditory performance. An unloaded M4 carbine will be checked out by study soldier support for use in this task. HRVs will be asked to clear, disassemble, assemble and perform a functions check (Department of the Army, 2019a) as described below.

Clear and Disassemble:

HRV will start with the weapon in the low ready.

1. Clear the weapon.
 - a. Point weapon in safe direction, ensure it is on SAFE, and remove the magazine.
 - b. Lock the bolt open and return charging handle to the forward position.
 - c. Ensure the receiver and chamber are free of ammo.
 - d. Press the upper portion of the bolt catch to allow the bolt to go forward.
2. Disassemble the weapon, clearly separating the following parts, retaining sling and optics:
 - a. Lower receiver and upper receiver. Separated but connected by sling.
 - b. Charging handle and bolt carrier. Separated.
 - c. Bolt, firing pin, bolt cam, and firing pin retaining pin. Separated.
 - d. Buffer and buffer spring. Separated.

Time will stop when the HRV returns to the standing position with all parts of the weapon on the flat surface.

Assemble and Perform a Functions Check:

HRV will start from the last position in the previous task.

1. Assemble the weapon.
2. Perform a function check on the weapon.
 - a. Place selector lever on SAFE. Pull charging handle to rear and release.
 - b. Pull trigger. Hammer should not fall.
 - c. Place selector lever on SEMI. Pull trigger. Hammer should fall.
 - d. Hold trigger to the rear and charge the weapon.
 - e. Release trigger with a slow, smooth motion, until fully forward. An audible click should be heard.
 - f. Pull trigger. Hammer should fall.
 - g. For BURST weapons.
 1. Place selector lever on BURST. Pull charging handle to the rear and release.
 2. Squeeze trigger. Hammer should fall.
 3. Hold trigger to the rear. Charge weapon three times.
 4. Release trigger. Squeeze trigger. Hammer should fall.
 5. Charge the weapon again, place it on SAFE, and close the dust cover.
 - h. For AUTO weapons.
 1. Place the selector switch on AUTO. Pull charging handle to the rear and release.
 2. Squeeze the trigger. Hammer should fall.
 3. Hold the trigger to the rear and cock the weapon again.
 4. Fully release the trigger then squeeze it again. The hammer should not fall.
 5. Charge the weapon again, place it on SAFE, and close the dust cover.

Time will stop when the HRV returns to the standing position with all parts of the weapon on the flat surface.

Hearing protection device (HPD) fit testing (Arrival and departure test series).

Fit testing is an effective method of determining the magnitude and consistency of attenuation afforded by hearing protection (Murphy, Themann, & Murata, 2016). HRVs will wear custom earplugs produced using data returned by the ear canal scanning procedure (Stefanson & Ahroon, 2019). Fit testing, using the FitCheck Solo software (<http://www.michaelassociates.com/products/fitcheck-solo-tm/>) on a Dell 7540 PXIe cDAQ workstation with FitCheck ear muffs, will be completed to estimate attenuation (Figure 20). Differences between the occluded and unoccluded thresholds provide these estimates. The minimum acceptable attenuation for the HRV's right ear is 20 dB for the frequency range of 0.5, 1, 2, and 4 kHz. The FitCheck solo is based on a system developed and licensed from CDC/NIOSH HPD Well-Fit. HRVs will be asked to indicate when a tonal signal is heard with and without wearing the passive earmuff. It is expected that HPD Fit testing will be completed on days 2 and 3 of the arrival series, and during all departure series visits.



Figure 20. FitCheck headphones with 3.5 mm plug, and a screen shot of the FitCheckSolo software.

Otoacoustic emissions suppression (Arrival and departure test series).

Otoacoustic emissions (OAE) suppression will be examined during the arrival and departure series using the Etymotic ER-10 series otoacoustic emissions probe system. The amplitude of the cubic difference distortion product produced under simultaneous stimulation with two pure tone signals will be examined for evidence of a suppressive effect. Probe tip earphones will be placed in the test ear, and a moderate-level broadband noise (0.1 to 10 kHz, 60 dB SPL) will be presented to the contralateral ear via an ER4PT earphone. Two sinusoidal tones, F1 and F2, will be delivered to the probe at a F2/F1 frequency ratio of 1.22 and levels of 55- and 40-dB SPL at the F1 and F2 frequencies, respectively (Deeter, Abel, Calandruccio, & Dhar, 2009). The F2 frequency will be swept from 1.5 to 6 kHz at a rate of 0.11 octaves per second, and responses to 6 sweeps will be obtained (total sweep time < 4 min) with and without contralateral noise. The HRV will be asked to sit quietly while hearing the tones and noise. The levels of OAE suppression (i.e., the difference in OAE magnitude across contralateral noise conditions) will be evaluated as a covariate in changes in auditory performance.

Extended frequency hearing sensitivity (Arrival and departure test series).

Extended frequency hearing sensitivity using Bekesy audiometry will be completed during the arrival and departure series in the same manner and using the same equipment as previously described in section 8.9.4. Thresholds will be obtained bilaterally from 10 to 16 kHz inclusive.

Sound Field to ear-drum transfer function (Arrival and departure test series).

Sound field to ear-drum transfer functions will be obtained for each HRV during the arrival and departure series. The complex (real and imaginary) influences of the head and external ear on the signal reaching the tympanic membrane (eardrum) will be measured using a moderate-level (e.g., 70 dB SPL) pure tone swept between 0.1 and 8 kHz. A small flexible silicone probe tube (Figure 21) will be inserted into the HRV's ear canal to approximately 5mm from the tympanic membrane (TM) and attached to a probe microphone assembly (Etymotic Research ER7C) located just below the HRV's pinna. In addition, a reference microphone will be located near the HRV's head above the pinna. Results will be used to estimate differences between HRVs in the efficiency of sound energy transfer through the external ear. Insertion depth will be guided using an acoustic probe signal.



Figure 21. Etymotic Research ER7C probe microphone used to determine the sound field to ear-drum transfer function.

Startle response (Arrival and departure test series).

Startle responses among HRVs will be measured during the arrival and departure series. Short bursts (12 kPa peak, 100 ms) of medical-grade nitrogen gas will be delivered to the nares ipsilateral to the HRV's left ear. A custom helmet similar to that found in Figure 22 will be used to present the air puffs at a consistent location and distance from the nares. The magnitude, latency, and habituation of the startle response will be evaluated as a covariate of changes in auditory performance. The startle response will be quantified using surface electromyography (EMG), a procedure described in Section 8.9.20.



Figure 22. An example of a custom helmet with movable arms used to present short duration puffs of medical-grade nitrogen to areas on the face.

Neurocognitive assessment (Arrival and departure series, Dose administration series).

HRVs will complete a brief neurocognitive assessment involving a Go/No-Go task and a Sternberg Memory Search task from the Defense Automated Neurobehavioral Assessment (DANA) (Lathan, Spira, Bleiberg, Vice, & Tsao, 2013). HRVs will use a PC with a keyboard and mouse to input their responses. The DANA demonstrated adequate reliability over test-retest (Lathan et al., 2013; Russo & Lathan, 2015) and across testing environments (e.g., arctic, jungle, high altitude, desert shipboard) (Haran, Lovelace, & Florian, 2015; Lathan et al., 2013). In the Go/No-Go task, HRVs are asked to attend to a house displayed with several windows (Figure 23, left panel). Periodically, a “friend” or “foe” appears in a random window and the HRV is asked to click the mouse when a “foe” appears. This task assesses decision making, sustained attention, and impulsivity. This task takes approximately 2 minutes to complete. In the Sternberg Memory Search task, HRVs are initially asked to memorize a set of five letters displayed on the screen (Figure 23, right panel). After memorizing these five letters, individual letters display on the screen and the HRV is asked to categorize whether the displayed letter is a member of the initially memorized set. This task assesses working memory. This task takes approximately 5.5 minutes to complete.

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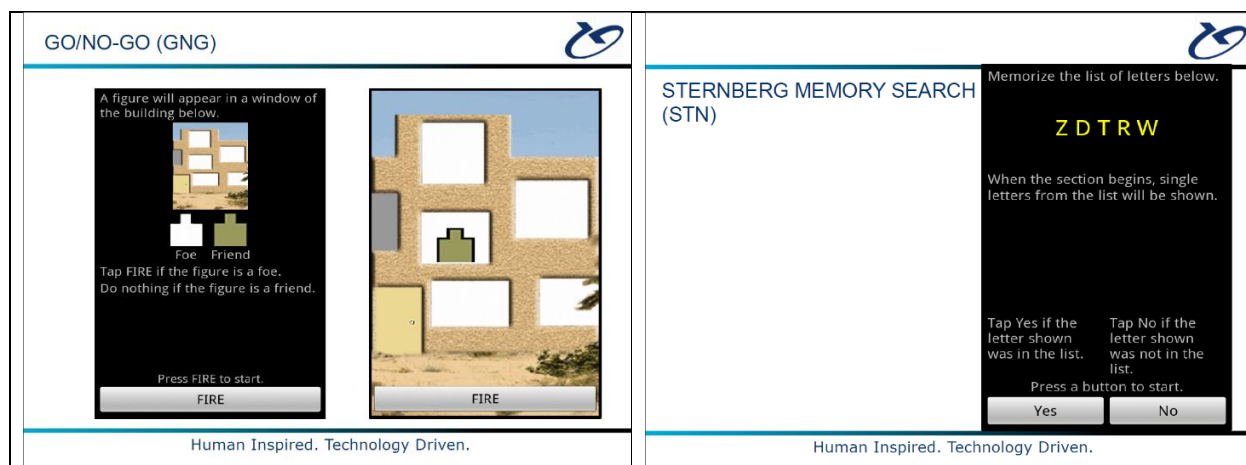


Figure 23. Screen shot examples of the Go/No Go and Sternberg Memory Search portions of the Defense Automated Neurobehavioral Assessment (DANA) (Lathan, 2015).

Alcohol screener (Daily test series).

Breath alcohol content (BAC, using an Expired Breath Alcohol Content screener and disposable single-use mouthpiece) will be screened at the start of each daily test series using the AlcoMate Revo Breathalyzer. This device is approved by the U.S. Department of Transportation. The goal of this testing is to ensure that HRVs are not providing continued consent to participate under degraded decision-making capacity, to avoid the potential increased susceptibility to TTS following recent alcohol consumption (Kraaijenga, van Munster, & van Zanten, 2018), and because alcohol impairs motor function, attention and cognition, and disrupts ABR responses and DPOAEs (Hwang, Tan, Chiang, & Liu, 2003; Upile et al., 2007). HRVs will be asked to blow steadily and forcefully into the screener single-use mouthpiece for at least 6 seconds. This information will also be used as a correlate of auditory system performance (e.g., acoustic reflexes, tinnitus). Any BAC result indicating a blood alcohol concentration exceeding 0.046%, will lead to a re-test in a private room at the end of the visit to rule out any effects of an oral rinse (e.g., mouthwash) containing alcohol. If the prior result is confirmed on retest with a different breathalyzer device, the HRV will not be permitted to access the field site to take part in the dose administration series on that day. The retest will be considered confirmed if the BAC result exceeds 0.035%, assuming slow alcohol metabolism and a 1-hour interval between tests. The volunteer will be dismissed from the study if the limit of 0.05% is exceeded on two separate days.

Daily questionnaire (Daily test series).

A series of daily questions (Appendix 6) will be administered at each daily test series. Questions examine HRVs current self-reported status of hearing, ears, tinnitus, dizziness, possible adverse events, and activities done recently that may explain changes in the current test results. The daily questionnaire will include the HRVID and no PII.

Standing balance (Daily test series).

One condition of the modified Romberg Test of Standing Balance will be used to screen for subtle changes in balance function associated with the noise exposures administered in this study. The modified Romberg test was developed for use in the National Health and Nutrition Examination Survey (NHANES), which is conducted by the U.S. National Center for Health Statistics with support from the National Institute on Deafness and other Communication Disorders. A gait belt with an attached 3D accelerometer will be worn by HRVs. HRVs will be asked to stand on a foam pad near a wall, with feet together, arms crossed, and eyes closed. Once in position, HRVs will be asked to turn their heads back and forth (approximately 30 degrees) at a rate of one sweep per second and maintain balance without moving arms, feet, or opening eyes for 30 seconds. The foam pad is used to reduce proprioceptive cues, and eyes are closed to eliminate visual cues. Timing information and accelerometer information will be used to monitor for changes in balance function. The standing balance procedure will take place during each daily test series.

Thresholds in noise (Daily test series).

The thresholds in noise test, occurring during each daily test series, provides a determination of the masking effect of a broadband (0.2 to 8 kHz) noise on the audibility of tones. A filtered white noise will be presented at a level of 70 dB SPL through RadioEar DD450 circumaural earphones. HRVs will be asked to perform a process similar to the assessment of hearing sensitivity procedure, wherein they will activate the pushbutton whenever they can hear the tone and release the pushbutton when the noise masks the tone. This test will be monitored as a potential indicator of possible synaptopathy/threshold-independent hearing disorders (Ridley et al., 2018) and will be evaluated as a covariate of changes in auditory performance. Additional equipment used includes the VIAcoustics Bekesy Pro license software installed on a National Instruments (NI) PXIe-based data acquisition system.

Frequency modulation detection threshold (Daily test series).

The frequency modulation detection threshold (FMDT) test is a measure of temporal processing ability (Kamerer et al., 2019). HRVs will be asked to determine changes in the detectability of modulations in the frequency of a tonal signal. The threshold is the minimal excursion in modulation detected. A three-alternative forced-choice (3AFC) procedure will be used to determine the threshold of detection for sinusoidal frequency modulations for a 1.5 kHz carrier tone presented at 70 dB SPL. Signals (0.75 second duration) will be presented in three intervals. One randomly-selected interval will contain a modulated tone while the others will contain steady tones. The detection threshold will be based a transformed up-down method. HRVs will be asked to sit quietly in a comfortable chair and to choose which tone they believe is frequency modulated. The data will be collected using custom MATLAB software controlling National Instruments (NI) PXIe-based data acquisition system and stimuli delivered to RadioEar DD450 circumaural headphones. This test, conducted during each daily test series, will be monitored as a potential indicator of possible synaptopathy/threshold-independent hearing disorders (Kamerer et al., 2019) and will be evaluated as a covariate of changes in auditory performance.

Auditory evoked potentials (Daily test series).

Auditory evoked responses will be completed during each daily test series. These include auditory brainstem responses (ABR) and ECochG, common clinically performed tests assessing the function of the cochlea, auditory nerve, and lower auditory regions of the brain. These tests will be monitored as a potential indicator of possible synaptopathy/threshold-independent hearing disorders (Bramhall et al., 2017; Kameron et al., 2019; Ridley et al., 2018) and will be evaluated as a covariate of changes in auditory performance. Sensors will be placed on the skin during the sensor management section (Figure 25). Gold foil Tiptrode® sensors (Figure 24) will be placed in each ear (Figure 25, EAC1 and EAC2 locations) just prior to the test. Signaspray®, a conductive spray used for high-conductance electrode placement, will be used to improve conductivity of the Tiptrode® in the ear canals.

During testing, HRVs will be asked to adjust a reclining chair to be comfortable for sitting with little or no movement during a test period of up to 15 minutes. Stimuli (tone bursts at 1.5 and 4 kHz, 110- and 103-dB peak-equivalent dB SPL, respectively) will be permuted randomly to ensure uniform data acquisition across combinations of stimuli and ears. Presentations will continue until an average from 1500 artifact-free presentations have been obtained for each stimulus, or until 15 minutes of stimulus acquisition have elapsed, whichever happens first. This corresponds to a maximum of 1,875 presentations per stimulus. Following data collection, the sensors will be gently removed from the HRVs ear canals and locations on the skin. The protocol for monitoring potential indicators of possible synaptopathy/threshold-independent hearing disorders is informed by Kameron et al. (2019). Data will be obtained using custom Matlab scripts controlling National Instruments (NI) PXIe-based data acquisition system, with signals routed into the ear canal via ER-3A insert earphones and Tiptrode® sensors (Figure 24). The electrophysiological signals from the Tiptrode® sensors and other evoked response electrodes will be routed through independent channels on an Intelligent Hearing Systems Opti-Amp system.



Figure 24. Example of the foam insert earphone tip wrapped in gold foil (i.e., a Tiptrode®) inserted into the outer portion of each ear canal during evoked response testing.

Sensor management (i.e., the connection of body worn electrodes) is included early in the daily test series to ensure adequate time for the electrode-skin interface to reach minimal impedance. This “settling” time facilitates high-quality signal acquisition in subsequent procedures. Sensors used during AEP testing will be placed on the HRV during the daily test

sensor management period. Sensors (surface electrodes) will be attached to the skin surfaces at each mastoid, the top of the head at midline, and the forehead at midline (Figure 25, M1 and M2, Cz and Fz, respectively). NuPrep Skin Prep Gel, a conductive skin gel commonly used to lower impedance and improve signal quality, will be used to attach the sensors to each location on the skin. Sensors will be held in place with medical-grade hypoallergenic adhesive tape. The sensors pick up electrical energy produced by the auditory nerve and auditory brainstem in response to sound presented in the ear.

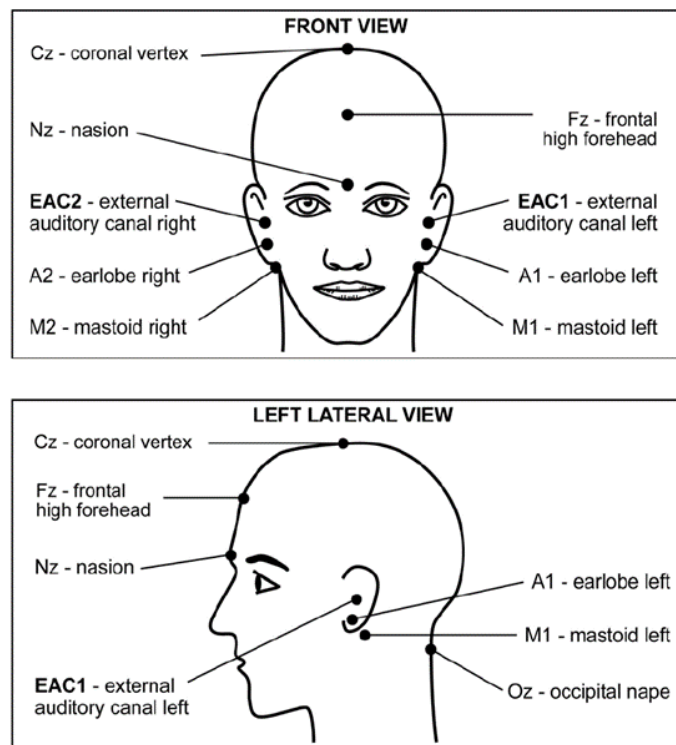


Figure 25. Sensor and electrode placement during auditory evoked potential (AEP) testing. Figure obtained from <https://usermanual.wiki/Vivosonic/V50.USERS-MANUAL-2/html>, accessed 08/13/2020.

Tinnitus loudness (Daily test series, Dose administration series).

Immediately upon completion of the hearing sensitivity evaluation, the automated software will present a recorded voice asking: “*Right now, do you hear any sounds in your ears or head?*” If the HRV indicates current tinnitus, the tinnitus loudness evaluation will proceed. This will be completed to obtain objective measurements of tinnitus loudness throughout the study and will be evaluated as a covariate of changes in auditory performance. Changes in tinnitus loudness will be assessed bilaterally using a noise matching the spectral shape of the HRV’s most recent hearing sensitivity at each stimulus frequency. The spectrum will be interpolated between stimulus frequencies. The 1/3-octave band spectrum will match the nearest available data at frequencies below and above the frequency range. The HRV’s task will be similar to the assessment of hearing sensitivity, the HRV will depress the response switch when

the ringing or other ear noise is heard (i.e., to increase the level of the noise) and will release the response switch whenever the noise has rendered the ringing or other noise inaudible. The initial 1/3-octave band levels of the threshold-shaped noise will be -10 dB relative to the listener's threshold. This testing will be completed using the VIAcoustics Beksy Pro license software installed on a National Instruments (NI) PXIe-based data acquisition system, and HRVs will wear RadioEar DD450 circumaural headphones during the test.

Monitoring Head/Neck Activity (Arrival Series and Dose administration series).

Concomitant muscle activity of the head and neck can elicit middle ear muscles contractions (Tasko et al., 2018) and therefore potentially impact exposures at the ear during the dose administration series. There muscle activity from selected muscles of the head and neck will be monitored. Surface electromyography (EMG) recordings will be made using a Delsys Bagnoli® 8-channel Desktop system and Delsys 2.1® reusable active electrode sensors (Delsys, Natick, MA). EMG signals will be amplified by 60 dB and band-pass filtered (20-450 Hz) prior to analog-to-digital conversion. EMG sensors (Figure 26) will be attached bilaterally over the orbicularis oculi (OOC) muscles, the masseter (MAS) muscles, the suprahyoid complex (SPH), and the sternocleidomastoid (SCM) muscle on the side of the neck using double-sided, medical grade, hypoallergenic adhesive (Figure 27). Standard procedures will be used to identify the location to place each electrode sensor (Criswell & Cram, 2011).

Staff will gently clean the small locations on the skin required to place electrode sensor using disposable alcohol wipes. Medical-grade hypoallergenic adhesive tape will be used to remove loose skin cells and debris in the sensor placement areas. HRVs will be asked to notify staff of any discomfort during the sensor site preparation and placement. Following electrode placement, the validity of EMG recordings will be verified by having HRVs tightly close the eye (OOC), clench the jaw (MAS), forcefully pressing the tongue against the roof of the mouth (SPH), and turning the head (SCM).

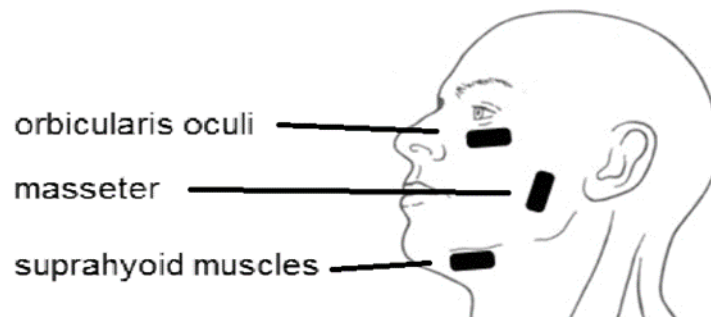


Figure 26. EMG sensor locations on one side of the face. The SCM muscle is outlined on the neck.



Figure 27. Delsys Bagnoli electromyography (EMG) sensor and double-sided, medical grade adhesive used to attach sensor to skin during startle response test and dose exposure series. (Note: the length of each conductive bar is 10mm.)

Monitoring HRV arousal (Daily test series and Dose administration series).

During the dose administration series, arousal level will be monitored using selected cardiovascular and electrodermal measures. Pulse oximetry and pulse rate will be obtained using the Biopac Oxygen Saturation Amplifier, Biopac Blood Oximetry Transducer. These devices measure beat-by-beat, blood oxygen saturation levels and heart pulse rate in a noninvasive fashion. Skin conductance measures will also be obtained via the Biopac Electrodermal Activity Amplifier and Transducer. A Biopac Power Supply will deliver isolated power to the Biopac transducers and amplifiers. HRVs will be asked to wear noninvasive sensors on their non-dominant fingertips. Measures of heart rate, heart rate variability, and skin conductance levels will also be used as covariables to changes in auditory performance. These measures will be collected during the daily visit and the dose administration and results will be used as a covariate for auditory performance.

Protecting the non-test ear (Dose administration series).

HRV's will wear a custom full shell earplug as hearing protection in the right ear during the dose administration. The fit and attenuation of the custom earplug will have been verified during the HPD fit testing protocol (arrival series), and trained technicians will insert the earplug properly. A probe for measuring OAEs will be embedded in the custom earplug while 3D printing. This probe will be configured to produce a two-tone complex for monitoring OAE magnitude throughout the exposure series, with particular interest in changes to the amplitude of the cubic difference product ($2f_1-f_2$) during the time surrounding each exposure. A protective earmuff will be placed over the custom earplug in the non-test ear. The use of a custom earplug and double-protection (the custom earplug and the single-sided earmuff) is a safeguard. The likelihood that both protectors will fail is considerably lower than either one alone.

Distraction task during noise exposure (Dose administration series).

During the dose administration series, HRVs will be engaged in a task to ensure that overall study results are not unduly influenced by cognitive factors. The cognitive task will

involve responses to visual stimuli (i.e., arithmetic problems) using a computer screen and mouse. Performing the task requires a series of single mouse clicks to minimize movement of the head and upper extremities during the impulsive noise exposures.

Behavioral monitoring (Entire residential stay).

Environmental noise exposure, recreational earphone noise exposure, sleep patterns, and heart rate information during the non-test period will be logged using the Apple® iPhone, iWatch, and AirPods. Data will be visualized using the software application developed for the University of Michigan/Apple Hearing Study (Neitzel et al., 2020), captured as a screenshot, and converted to numerical data using MATLAB® image processing software. Basic heart rate information may also be obtained from the Apple Health app (Figure 28). All Apple devices will be registered to the project and issued to HRVs to protect anonymity. HRVs will be assigned an Apple iWatch, iPhone and AirPods upon arrival to the study site, and will be asked to wear the iWatch consistently, and to use the iPhone and AirPods when listening to music using headphones. This will allow the study staff to track the level and amount of noise exposure during the non-test period. This information will be used as a covariate for changes in auditory performance, and may help to explain changes in daily test performance. Data will be captured at each daily visit and logs will be downloaded during the sensor management portion of the daily test series.

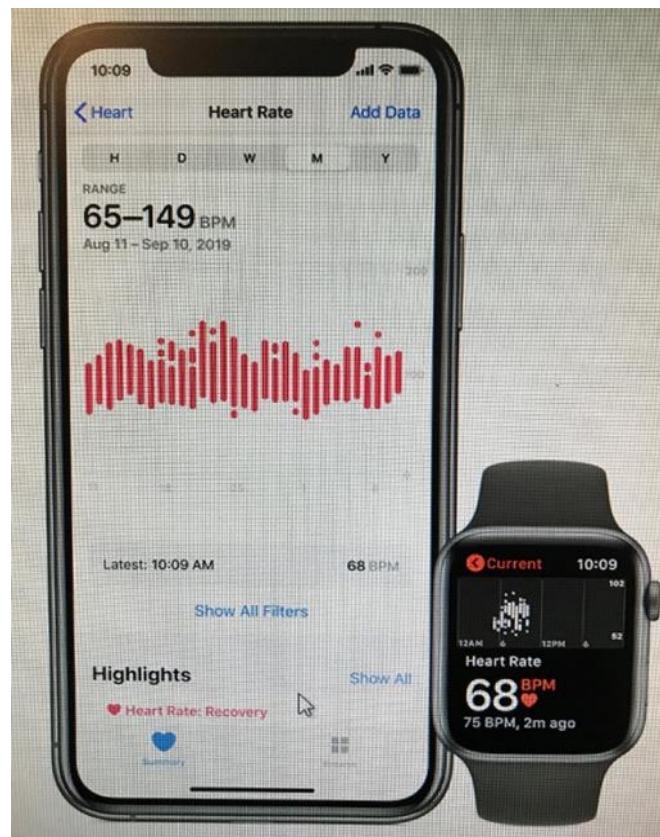


Figure 28. A screen shot example of the Apple iPhone and iWatch Health app heart rate data. A screen shot will be taken and results will be converted to numerical data using MATLAB processing software.

Adverse Event Assessments

Expected Adverse Events

The potential adverse events monitored in this protocol are:

- Hearing impairment
- Bothersome tinnitus
- Balance/vestibular system changes
- Cochlear synaptopathy
- Neurocognitive changes (working memory, sustained attention, impulsivity)

Hearing impairment.

It is very unlikely that this research will induce a permanent hearing impairment. The study is designed to estimate the MTD for impulses and select the DRC that comes closest to the MTD without exceeding it. The MTD is defined as the impulse noise dose (i.e., combination of impulse energy level and number of repetitions) that is known, with greater than 95% confidence, to protect 95% of Service Members from sustaining a TTS at 2 minutes post-exposure of 25 dB or more at any frequency between 0.5 and 8 kHz. If an HRV sustains a TTS of this magnitude, all noise doses at and above that dose within that stimulus class (i.e., all impulse levels greater than the one producing the criterion TTS, all repetition numbers equal to or greater than the current number at the current energy level) are closed to further HRVs. Additionally, the observation of a 15 dB TTS that persists for 24 hours following the exposure will also be considered a criterion TTS.

Using the U.S. National Cancer Institute Common Terminology for Adverse Events, version 5 (CTCAEv5), a threshold shift of 15 dB or greater will be reported to be an adverse event if it persists throughout the departure test period (3 test days post-exposure). The definition of hearing impairment in CTCAEv5 is a threshold shift of 15 to 25 dB averaged at two contiguous frequencies between 1 and 8 kHz (Grade 1), or greater than 25 dB averaged at two contiguous frequencies (Grade 2) in at least one ear. TTS is known to recover over time (Chan et al., 2016; Ward, 1960), and under the pessimistic assumption that two audiometric frequencies are maximally affected and the HRV sustaining the TTS has atypically slow TTS recovery rates, recovery from TTS magnitudes of 25, 35, and 50 dB to less than 15 dB would be expected to occur within 24, 42, and 70 hours, respectively. An observation of an HRV exhibiting a slow recovery from a 15 dB TTS prevents additional HRVs from being exposed to the level producing that TTS.

HRVs that exhibit a criterion TTS, will not return to the field site, will be advised to minimize additional noise exposure (e.g., music listening or exposure to other loud noises), and will enter the departure series protocol the following day. The long-term implications of a grade 1 adverse event would likely include continued recovery toward baseline hearing sensitivity, but without confirmation of a return to that level by the end of the departure series. If one assumes that the TTS is maximal at 3 and 4 kHz, and recovery halts permanently at 15 dB, and the Service Member's baseline hearing sensitivity was at the limit of eligibility for the study, the Service Member would remain within the criteria for an H1 ("Normal") hearing profile and

readiness would not be impacted. Unless multiple safeguards fail the HRV's right ear will have had the protection of two hearing protectors during all exposures, and there would be no reason to expect that the hearing in this ear would have been impacted by the exposures. The Service Member would also meet the criteria of having "no impairment" according to the World Health Organization (Olusanya, Davis, & Hoffman, 2019), the American Medical Association (2008), and the Global Burden of Disease Expert Group on Hearing Loss (Stevens et al., 2013).

Bothersome Tinnitus.

Estimates of the likelihoods of these adverse events are gross, at best. The likelihood of bothersome tinnitus is 1.5%, based on our analyses of the percent of the non-institutionalized U.S. population, ages 20-29, with "Excellent" or "Good" self-reported hearing that has fired between 1,000 and 50,000 rounds from a firearm. Given that the tinnitus will be monitored multiple times daily while the HRV is at the study site, the exposures to the HRV will be halted before research-related tinnitus will limit instrumental activities of daily living (ADL), thus we would expect no greater than Grade 1 severity (re: CTCAEv5) from this event following the recovery period. Acute tinnitus associated with noise exposure is reversible (Chermak & Dengerink, 1987) and is expected to recover within a few days. HRVs meeting the criteria for an adverse event due to bothersome tinnitus (i.e., two consecutive responses indicating increase from baseline self-reported tinnitus score by 5 or more units and, at least one response indicating that tinnitus has become a "moderate" or greater problem), will not return to the field site, will be advised to minimize additional noise exposure (e.g., music listening or exposure to other loud noises), and will enter the departure series protocol the following day. Noise-induced tinnitus, and recovery from it is common, and there are no long-term implications for HRVs experiencing bothersome tinnitus that would result from the procedures in this study. Tinnitus, however, is a multifactorial phenomenon, so if the tinnitus was coincidental to participation in the study, medical evaluation of potential causes (e.g., dietary factors, caffeine, nicotine, fatigue, other health conditions) may be suggested to the HRV if symptoms have not remitted by the end of the 3-day departure series.

Balance/Vestibular system changes.

Recent research has revealed that there is a need to expand the range of symptoms monitored following exposure to impulsive noises. Outcomes such as headache, "long think" (i.e., slow reaction time), lightheadedness/dizziness, tinnitus, frustration, and irritability have been observed among grenade instructors positioned in a protective pit, with increased symptoms following exposure to the impulsive noise (e.g. Sajja et al., 2019). The acoustics of a grenade impulse differ substantially from a small arms impulse, especially for personnel located in a protective pit. The initial pressure wave for small arms (i.e., the interval between the onset of the waveform and its first crossing through ambient pressure) is between 200 and 500 millionths of a second, while the pressure wave for the Service Members in Sajja et al., (2019) was approximately 5 thousandths of a second. This acoustical difference implies that the grenade signal would transfer a greater amount of energy into the Service member's body. However, the peak pressure levels of the impulses in this study were between 154- and 163-dB SPL, which are in the range of peak levels for military small arms.

It is plausible that the noise exposures used in this protocol could alter vestibular function. However, it is unlikely that those effects would occur at energy levels lower than the MTD in this research, especially given that the issue has only recently gained attention and small arms have been in common use for quite some time. Further, Service Members operating small arms are physically coupled to the weapon (e.g., through the “cheek weld” during sighting), which delivers vibrational energy with much greater efficiency than for an acoustic signal.

Most of the literature involving human subjects in this area is cross-sectional, implies exposures well above the levels necessary to produce a criterion TTS, and merges impulse, impact, and high-level continuous noise exposures (e.g., Golz, et al. 2001). Studies with animal models (e.g., Stewart, et al, 2020; Perez, Freeman, Cohen, & Sohmer, 2002) often involve exposure levels, durations, susceptibility, and frequency spectra (re: the animal’s auditory sensitivity curve) (e.g., Turner et al., 2005) that differ widely from those used in the current study.

In order to identify subtle changes to vestibular function, this protocol includes a “sharpened” condition of the Romberg test of standing balance. The sharpened standing balance condition involves the minimization of proprioceptive cues (standing on a foam pad) and visual cues (eyes closed), and assesses vestibular performance by asking participants to perform a slow horizontal head shake for 30 seconds. Performance will be measured as pass/fail (re: balance maintenance for 20 seconds or more), measuring time until the HRV changes opens their eyes, moves their arms, or changes stance to maintain balance, and through monitoring sway and acceleration of an accelerometer mounted on a gait belt that will be worn for safety purposes. This condition may reveal occult changes in balance and vestibular function (Cohen, 2019). In addition, we include self-reported dizziness and loss of balance as part of the Neurobehavioral Symptom Inventory (NSI) (Caplan et al., 2010). For the purposes of this study, an adverse event involving the vestibular system will be defined jointly as an HRV report of “feeling dizzy” or “loss of balance” that worsens from NSI baseline performance by 2 score units (on a 5-unit scale), and a reduction in the time to fail on the sharpened Romberg test below the HRVs 95% confidence interval established through baseline testing. Alternately, an observation of frank unsteadiness by the field site technician following dose administration will also be classified as an adverse event involving the vestibular system.

Recovery from a noise-induced disturbance in vestibular function is expected, based on studies with animal models. In the guinea pig, the recovery of vestibular function occurs more rapidly than for auditory function (e.g., Fetoni, et al., 2009). We expect no worse than grade 1 severity re: CTCAEv5, with no limitations of instrumental ADL. Short-term management of subtle effects identified through the NSI items and the sharpened Romberg test will include advising rest, halting additional exposures for the HRV, and monitoring symptoms during the departure series, which will begin the next test day. If the adverse event is identified by the technician as unsteadiness following the dose administration procedure, the technician will instruct the HRV to sit down and rest for a moment. The site manager will then be contacted and they will ask the HRV to describe their symptoms. If the HRV’s symptoms have not improved following a 10-minute rest period, the event will be considered a medical emergency requiring paramedic support. This would be considered a Grade 2 adverse event. No significant long-term

implications are anticipated from these study procedures. Medical follow-up will be advised if symptoms worsen or do not abate before completion of the 3-day departure series.

Cochlear synaptopathy.

The term “cochlear synaptopathy” was recently coined to represent a condition wherein the synapse is lost between the dendrites of the auditory nerve and the inner hair cell, which is the cochlea’s sensory transducer. This phenomenon has been shown in studies with multiple mammalian animal models (Liberman & Kujawa, 2017). However, research in this area is in its infancy. The exposure types, numbers, and signal characteristics necessary to produce cochlear synaptopathy remain unknown (Fernandez et al., 2020). Some researchers in this area (Liberman & Kujawa, 2017) have taken the position that damage to the synapse occurs at a lower threshold than that for damage to the cochlear outer hair cells, although this position could be controversial because it suggests that the vast majority of people with hearing loss also have cochlear synaptopathy.

A TTS-based approach is often used to study cochlear synaptopathy in animal models. In this approach, the animal model is subjected to a high-level noise for a period of time, typically hours, and TTS estimates are obtained through electrophysiological testing (e.g., ABR). Testing typically commences 24 hours after exposure and continues until thresholds return to baseline, which can be weeks later. The magnitudes of the TTS in the animal models at 24 hours post-exposure are frequently approximately 40 dB. In male CBA/CaJ mice, recovery from TTS followed a slope of approximately 33 dB/log(minutes), indicating that thresholds would be expected to recover by about 33 dB between 2000 and 20,000 minutes (Kujawa & Liberman, 2009). Linear TTS recovery as a function of log time is also expected in humans (Chan et al., 2016).

A single, accurate, assay of cochlear synaptopathy applicable to living human subjects has yet to reach acceptance. The approach taken in this protocol will be to monitor cochlear synaptopathy involves the use of multiple methods, which include two electrophysiological tests (ABR, ECochG) and two psychophysical tests (Thresholds in noise, Frequency modulation threshold) and requirement of consistent and significant changes from baseline on at least two measures to declare that this adverse event has occurred.

An estimate of the likelihood of cochlear synaptopathy in this research is difficult to produce, but it is reasonable to expect that it would be uncommon because the criterion TTS in this research is much lower than the TTS values produced in studies of cochlear synaptopathy in animals. For example, if one applies the 33 dB/log (minutes) slope to a TTS of 40 dB measured 24 hours post-exposure, one would expect that the TTS was approximately 65 dB at 300 minutes, and 98 dB at 30 minutes. The criterion TTS in this study is 25 dB at any single frequency. The results of Carter and Kryter (1962) demonstrate that among the HRVs sustaining the criterion TTS, it is reasonable to expect that the TTS magnitude will be between 25 and 35 dB.

In terms of severity re: CTCAEv5, cochlear synaptopathy could be coded as an acoustic nerve disorder not otherwise specified (#10000521) or an ear/labyrinth disorder - other

(#10013993). Under either classification, the severity would be grade 1 because the symptoms would be expected to be asymptotic/mild (i.e., at or and intervention is not indicated).

Neurocognitive changes.

The results of Sajja et al. (2019) support the notion that impulses from grenades with peak levels in the vicinity of 154 to 163 dB SPL could yield neurocognitive effects. Despite the substantial differences in the acoustic characteristics of the impulses produced by grenades and the small arms-like impulses in this research, we have elected to monitor for research-related neurocognitive changes. Although empirical estimates of the likelihood of such changes from procedures similar to those in this study do not exist, we reasoned that the likelihood is low, given the extent that small arms are used in the military. For example, the qualification procedures for the M249 (Squad Automatic Weapon, SAW) involve the discharge of approximately 800 rounds of 5.56 mm ammunition (Department of the Army, 2017), without consideration of the training preceding qualification with the weapon system. It seems reasonable to presume that the effects would be noticeable if the M249 crew exhibited symptoms similar to those found among grenade training personnel. We reason that it is very unlikely that the procedures used in this study will induce neurocognitive changes.

An adverse event involving neurocognitive changes will be defined as a sustained (two consecutive occasions) decrement beyond the 95% confidence limit on at least one of two behavioral measures (Sternberg Memory Search, Go/No-Go task), and a sustained decrement beyond the HRV-specific 95% confidence interval on the Somatic/Sensory or Cognitive subscales of the Neurobehavioral Symptom Inventory (Caplan et al., 2010). The severity of events meeting this definition would be Grade 1 (re: CTCAEv5), indicating a mild effect. We anticipate that the effects of the exposures on these variables would be reversible. Short term management would include closing the stimulus class to exposures at the current energy level and number of repetitions, plus at all higher energy levels, which will prevent the affected and all other HRVs from this exposure. In addition, the HRV will be instructed to rest for at least 24 hours prior to entering the departure series (3 test days). No long-term implications are expected.

Unexpected Adverse Events

Unexpected adverse events will be ascertained by self-report from the HRV on a daily basis (“Have you had any health problems since your last visit? If yes, please describe them.”). As a safeguard against unreported unexpected adverse events/unanticipated problems, personnel are assigned 1:1 to the HRVs at the field site to facilitate protocol adherence and identify any deviations or indications of adverse events.

If the unexpected event or problem indicates a need for emergency care, obtaining this care (e.g., paramedic support) will be the top priority. The procedure for reporting suspected unexpected adverse events will include reports to the site managers within 1 hour of the observation, collation of relevant data (e.g., test results, acoustical measurements of exposures, calibration records, as applicable) by site managers within 5 hours. The combined information will then be submitted to the available key study personnel, who will examine the information

and reach a provisional decision about whether the event could be reasonably attributed to study procedures or potentially affects the safety, rights, or welfare of current participants.

A three-category scale (“probably related,” “possibly related,” “probably not related”) will be used to gauge whether the event or problem was related to study procedures. Event severity will be estimated using the U.S. National Cancer Institute Common Terminology for Adverse Events, version 5. This severity system grades events on a 1 to 5 scale. In general, events or problems fall into Grade 1 if the affected HRVs are asymptomatic, report only mild symptoms, do not require intervention, and do not experience limitations to instrumental ADL. The grades progress through increasing degrees of ADL limitations, needs for intervention, and threats to life. Grade 5 is reserved for events or problems resulting in death.

All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the Human Research Protection Office (HRPO). A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Development Command, ATTN: FCMR-RP, 810 Schreider Street, Fort Detrick, Maryland, 21702-5000.

Study Discontinuation and Participant Discontinuation/Withdrawal

Prior to providing informed consent, all potential volunteers will be informed that participation in this research is voluntary and they may discontinue participation and withdraw their data from analysis at any time. Arrival, departure, and daily test series provide additional opportunities wherein HRVs will be specifically asked to affirm consent or provide informed refusal/withdrawal of consent to participate further in the study before traveling to the field site. Prior to the dose escalation series, the HRV will again be reminded of the voluntary nature of the study, and asked to confirm continued assent to participate or provide informed refusal/withdrawal of consent. For HRVs completing the study, they will have been asked to provide continued informed consent on at least 22 occasions, meaning they will have had at least 22 chances to provide informed refusal/withdrawal of consent from further participation in the study. These questions will be designed in a way that does not introduce coercion, bias, or influence. In the event that an HRV elects to withdraw from the study, study personnel will remind the HRV that he/she may choose to withdraw immediately, or he/she may choose to withdraw from the dose escalation series only. If the HRV chooses immediate withdrawal, the decision will be documented, the HRV will be released from the study, and assignment to their next duty will be facilitated without prejudice. The decision to withdraw from the study will in no way reflect negatively on the Service member’s record. If the HRV chooses to withdraw from the dose escalation series only, they will exit the exposure period of the protocol and begin the departure series. An experienced NCO (E-5 or E-6) will serve as ombudsperson to prevent coercion.

Additionally, the investigator may dismiss an HRV from participating in this research if circumstances arise which warrant doing so. These circumstances may include, but are not limited to, bothersome tinnitus, TTS, exposure to high levels of noise outside of the daily test periods, other activity outside of daily test periods that may interfere with the study, or inability

to complete portions of the study (e.g., poor test reliability). HRVs may also be dismissed from participating in the study because qualified HRVs exceed current study capacity. This information is included in the informed consent document.

Study Measures

Primary Outcome Measure

The primary outcome measure is TTS, which is based on comparison of post- dose administration hearing sensitivity test to baseline hearing sensitivity. Assessment of the primary outcome measure must occur immediately following each HRV cohort's daily post- dose administration hearing sensitivity test to examine for criterion TTS (≥ 25 dB TTS at any frequency between 0.5 and 8 kHz measured two minutes post-exposure). In the event of a TTS that is ≥ 15 dB and < 25 dB at any frequency between 0.5 and 8 kHz measured 2 minutes post-exposure series, data analysis will be conducted to determine whether hearing sensitivity has returned to within the 95% confidence interval of the baseline hearing sensitivity at the time of pre-exposure testing the following day. Immediate data analysis is necessary to determine if the primary objective endpoint for stoppage has been met.

Additional Measures

In addition to ongoing recordings of each impulsive stimulus at each HRV location, the study design includes multiple measurements upon arrival and before departure to obtain individual baselines, minimize learning effects during the exposure period, and detect subtle changes that might have occurred following the exposure period. Key variables measured multiple times per day during arrival, exposure, and departure periods include hearing sensitivity, video otoscopy, middle ear status, distortion-product otoacoustic emissions (DPOAE), simultaneous ABR and ECoG, thresholds in noise, frequency modulation threshold, standing balance, and tinnitus loudness for HRVs reporting tinnitus. Hearing sensitivity and tinnitus loudness (as appropriate) will be measured minutes before the first impulse presentation and starting two minutes after the final impulse presentation. HRVs will complete an arithmetic task throughout the impulse presentation period. Autonomic arousal as well as status of head/neck muscles will be monitored with bilateral electromyography sensors due to the strong link between the head/neck muscle activity and middle ear status (Tasko et al., 2018). The non-test ear will be occluded with an otoacoustic emissions probe monitoring for changes in DPOAE in the times surrounding the impulse, and a large-volume earmuff will be placed over that ear to provide additional attenuation and protection. Standing balance and neurocognitive function are included in the protocol to monitor for adverse events affecting these functions. A full list of measures is contained Tables 3-6.

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Table 3. Study Measures Included in Eligibility Determination Visit

Data Element	Source	Operational Specification
Demographic information	Eligibility determination visit	Age, gender, military occupation specialty (MOS), education, occupation, race/ethnicity <u>Variables:</u> Multiple individual items and scales
Ear and noise exposure history	Eligibility determination visit	History of ear related disease, self-reported hearing ability <u>Variables:</u> Multiple individual items
Noise and solvent exposure history	Eligibility determination visit	Lifetime Exposure to Noise and Solvents Questionnaire (LENS-Q): History of recreational, occupational, and military occupational noise and solvent exposures <u>Variables:</u> Multiple individual items and scales
Ear and noise exposure history	Eligibility determination visit	History of ear related disease (middle ear disorder, congenital abnormalities, dizziness), self-reported hearing ability <u>Variables:</u> Multiple individual items
Tympanometry and middle ear measures	Eligibility determination visit Daily test series	Middle ear function including wideband immittance at ambient pressure, wideband and conventional tympanometry and acoustic reflex thresholds Variables: Tympanometric peak pressure; static admittance; equivalent ear canal volume; tympanometric width; energy absorbance in 1/6-octave steps; ipsilateral and contralateral acoustic reflex threshold
Otoscopy	Eligibility determination visit Daily test series Pre-dose administration Post-dose administration	Visual assessment of pinna, ear canal and tympanic membrane <u>Variables:</u> Cerumen status; ear canal status; tympanic membrane status
Audiometry	Eligibility determination Daily test series Pre-dose administration Post-dose administration	Pure tone thresholds in dB HL from .5 to 8 kHz inclusive, including interoctave frequencies 3 and 6 kHz Extended frequency audiometry, including pure tone thresholds from 10 to 16 kHz will be completed during arrival and departure series only. <u>Variables:</u> threshold; TTS (derived)

Table 4. Study Measures Included in Arrival and/or Departure Series

Ear canal geometry	Arrival series, day 1	3-dimensional scan of concha and ear canal <u>Variables:</u> Ear canal cross-sectional area as a function of length; ear canal physical volume
Timed M4 field strip	Arrival series, day 2	Weapon familiarity, as indicated by time required to perform maintenance (field strip) on an M4 carbine. Arousal, as indicated by skin conductance, pulse rate and variability <u>Variables:</u> Time required for disassembly; time required for assembly; electrodermal activity; oxygen saturation in blood; pulse rate
Hearing protection fit testing	Arrival and Departure series	Assessment of hearing protection attenuation levels <u>Variables:</u> dB attenuation by frequency
OAE suppression	Arrival and departure series	Changes to DPOAE levels due to the introduction of a contralateral broadband noise stimulus <u>Variables:</u> Change in frequency-specific dB SPL of the cubic difference product
Sound field to ear-drum transfer function	Arrival series	Change in sound (magnitude and phase) between the external sound field and the eardrum <u>Variables:</u> Transfer function magnitude and phase in 1/6-octave bands
Startle/Electromyography (EMG)	Arrival and departure series (air puff) Dose administration (impulse)	Recordings of electrical activity of selected muscles of face, head, and neck <u>Variables:</u> Startle magnitude; cross-channel signal coherence; variance in tonic muscle activity
Neurocognitive Assessment	Arrival and departure series Pre-dose administration Post-dose administration	Changes in working memory, attention, impulsivity <u>Variables:</u> Working memory percent correct and response time; Go/No-Go percent correct, incorrect, no response, and latency.

Table 5. Study measures included in daily test series.

Daily questions	Daily test series	Subjective report of status (change in hearing, ringing, ear pain), sound exposure, recent smoking, etc. <u>Variables:</u> Multiple individual items and scales
Balance function	Daily test series	Time standing on foam with slow horizontal head turns without moving arms, feet, or opening eyes. <u>Variables:</u> Pass/fail at 20 seconds; time to fail (max. 30 seconds); sway area (horizontal plane); sway volume (3-dimensional)
Thresholds in noise	Daily test series	Detection of 1.5 and 4 kHz pure tones in the presence of a 70 dB SPL, 0.2 to 8 kHz broadband noise. <u>Variables:</u> Threshold in dB SPL; critical ratio in dB
Distortion product otoacoustic emissions (DPOAE)	Daily test series	Amplitude of the cubic difference distortion product (2F1-F2) <u>Variables:</u> Frequency-specific dB SPL of the cubic difference product
Frequency modulation detection threshold	Daily test series	Minimum detectable excursion in frequency for a 1.5 kHz carrier tone (750 ms duration, 70 dB SPL) <u>Variables:</u> Threshold for modulation detection
Auditory brainstem response (ABR) and electrocochleography (ECochG)	Daily test series	ABR and ECochG for tone-burst signals at 1.5 and 4 kHz <u>Variables:</u> ABR wave I peak amplitude, latency, and area; ABR wave V peak and latency; ECochG summing potential amplitude, action potential amplitude, cochlear microphonic amplitude
Tinnitus loudness	Daily test series Pre-dose administration Post-dose administration (Only HRVs reporting tinnitus)	Level of a threshold-shaped noise required to mask tinnitus <u>Variables:</u> dB in 1/3 octave band relative to threshold
Tinnitus information	Daily test series	Tinnitus and hearing related questions based on the Tinnitus and Hearing Survey <u>Variables:</u> Multiple individual items and scales

Table 6. Remaining Study Measures Included in Daily Test Series and Measures Included in Dose Administration Series.

Breath alcohol screener	Daily test series	Blood alcohol concentration <u>Variables:</u> % Blood alcohol concentration
Heart rate	Daily test series (download)	Average heart rate during period away from exam and field site, logged using wearable technology
Sleep duration	Daily test series (download)	Sleep duration during period away from exam and field site, logged using wearable technology
Continuous noise exposure	Daily test series (download)	Noise exposure during period away from exam and field site, logged using wearable technology
Exposure sound level	Dose escalation	Synchronous multichannel recordings of acoustic signals near each HRV <u>Variables:</u> Acoustic characteristics (peak, integrated level, 1/6-octave band spectrum) of each impulse received by each HRV; candidate DRC metrics and ANOR.
Skin conductance response, pulse oximetry and rate	Dose administration	Arousal, as indicated by skin conductance, pulse oximetry, and pulse rate and variability <u>Variables:</u> Electrodermal activity; oxygen saturation in blood; pulse rate

Data and Statistical Considerations

Data Processing and Quality Review

Study data pertaining to the study objectives (i.e., all data identified only using the HRVID, no PII) include hardcopy questionnaires and electronic files. Questionnaire data will be optically scanned and hand-entered by research technicians into a MATLAB structure data type that includes the database. The accuracy of data entry will be double-checked by a different technician. The technician identification numbers (TECHID) of both technicians will be included in the structure to facilitate this cross-check.

Electronic data will either originate as MATLAB variables (structures, tables, matrices, or cell arrays) or be transformed into those variable types. Review of the data for quality includes review of otoscopy recordings, examination of presentation/response histories (e.g., hearing sensitivity), artifact rejection effects (ABR, ECoG), and visual inspection to identify data profiles inconsistent with expectations that might indicate an error or protocol violation.

Sample Size Determination

This study is designed to accommodate a total of 7 cohorts consisting of a maximum of 64 HRVs (equal groups of 8 HRVs) completing the study (total $N = 448$). A maximum 40% attrition rate (due to ineligibility and withdrawals) of approximately 40% leads to a total possible enrollment of 632 HRVs. Each cohort will be presented only with increasing numbers of exposures for only one stimulus level and class. It is anticipated that these 7 cohorts can support DRC recommendations for at least two stimulus classes (quasi-free field and reverberant). The identification of an unsafe combination of stimulus class, level, and number of exposures (i.e., dose administration) will close that dose administration to additional testing with HRVs. Remaining HRVs in the specified cohort will continue the same stimulus class and level with only the planned lesser number of exposures. If a lesser number of exposures is found to be unsafe, that dose administration will close to additional testing with HRVs. This will continue until either the lowest number of exposures at a given stimulus class and level are deemed unsafe, or until all 64 HRVs have completed the study. The combination of stimulus class, level, and greatest safe number of exposures is sufficient to generate a DRC recommendation. If an unsafe combination is not seen among any HRVs in a cohort (within the specified combination of stimulus class and level) with the greatest number of exposures, the next cohort will be presented to increasing numbers of exposures using the same stimulus class and a higher-level impulse.

The two mandatory stimulus classes for this project are quasi-free field and reverberant settings because the quasi-free field stimulus class best represents firing range conditions and because the long envelope durations and complex waveform fine structure could uncover differences between DRCs that rely on integrated energy (e.g., LAeq8, LIAeq8) and those that rely on complex mathematical models (e.g., ICE, AHAH). Closure of one or more stimulus classes due to the identification of unsafe exposures will permit the addition of more stimulus classes (e.g., continuous + impulse noise).

The minimum number of HRVs required to reach 95% certainty of 95% population protection is 59. One confirmed criterion TTS in a group of 64 HRVs demonstrates that there is not 95% certainty of 95% population protection at a particular combination of stimulus class, stimulus level and number of exposures. The confidence that 95% of the population is protected, c , will be determined for each combination of stimulus class, level, and number of exposures (i.e., dose administration) via the following equation:

$$c = 1 - \sum_{i=0}^n \binom{N}{N-i} (0.95)^{N-i} (0.05)^i$$

Equation 1. Determination of confidence that 95% of exposed Service Members will be protected.

where c represents the confidence as a probability, N represents the total number of HRVs completing the dose administration and n represents the number of failures (i.e., HRVs who exhibit the criterion TTS during that dose administration). The observation of a single failure

within a cohort (max. size = 64) reduces the confidence in a safe exposure below 0.95 (Figure 29).

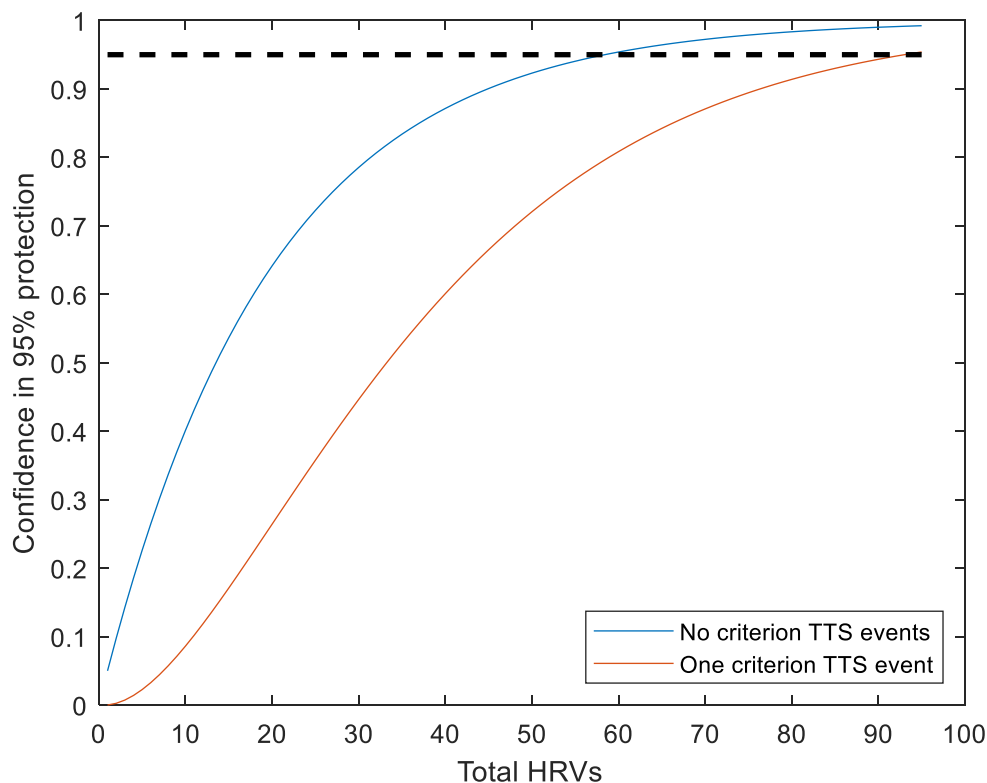


Figure 29. Confidence that 95% of exposed Service Members will be protected as a function of cohort size and number of criterion TTS events. A single criterion TTS event for cohort sizes up to 93 reduces confidence below 0.95. The minimum cohort size to reach 95% confidence is 59. The present study employs a cohort size of 64 as a safeguard against attrition.

Statistical Analysis

The primary objective of this project is to identify the DRC that comes closest to the MTD without exceeding it. The data used to determine the MTD for a given stimulus class are similar to those represented in Table 1. The MTD for a stimulus class is the exposure yielding less than 95% confidence that 95% of the military population will be protected from the criterion TTS. For the hypothetical data represented in Table 1, the MTD is 3 exposures. In cohorts including 92 HRVs or less, a single HRV sustaining a criterion TTS is sufficient to establish less than 95% confidence that 95% of Service Members will be protected (Figure 29). For the purpose of identifying the DRC that returns an ANOR closest to the MTD without exceeding it, ANORs shall be represented as integers by truncating decimal values (e.g., a predicted ANOR of 3.9 will be treated as 3 because it is impossible to be exposed to only part of an impulse).

Confidence that 95% of Service Members will be protected will be evaluated for all combinations of stimulus class, impulse energy level, and repetition number included in this research.

It is anticipated that the proposed study will return at least two MTDs, suggesting the possibility that two or more DRCs could be deemed appropriate. If different DRCs are selected across multiple stimulus classes, the final recommendation will be the DRC producing the ANOR that comes closest to the MTDs for all stimulus classes without exceeding them. Any DRC returning an ANOR exceeding any MTD will not be selected. Distance from the MTD will be represented by root-mean-square deviations between ANOR and MTD.

In addition to selecting a best-matched DRC for small-arms noise, analyses of factors correlated to TTS magnitude will be conducted. These analyses will involve fitting multilevel binary logistic regression models to observed TTS data. For example, this research is expected to obtain up to 31,360 estimates of TTS (i.e., difference in hearing sensitivity before and starting 2 minutes after dose administration) at the field site. The distribution of these TTS values is not expected to be normal, and the observed values will be dichotomized with a 10 dB TTS cut point. The multilevel binary logistic regression model will treat TTS values at each stimulus frequency as observations nested within ears, and ears as nested within HRVs. Potential covariates of TTS include stimulus factors (e.g., stimulus class, energy level, and number of repetitions), external ear acoustics (e.g., sound field-to-eardrum transfer function, ear canal geometry), middle ear acoustics (e.g., static admittance, wideband energy absorbance), cochlear mechanics (otoacoustic emission magnitude, contralateral suppression of otoacoustic emissions), other auditory/vestibular function (tinnitus masking level, standing balance performance), arousal/distraction (galvanic response, heart rate, pulse oximetry, startle response, performance on the distractor task), baseline hearing sensitivity, and multiple person-level variables (e.g., gender, race/ethnicity, length of service, firearm familiarity, exposure history). Regression models of this type can help identify modifiable factors involved in TTS.

The secondary objectives of this research explore the proposition that outcomes other than TTS (e.g., tinnitus, cochlear synaptopathy, standing balance function, neurocognitive status) are the first to show significant effects of small arms impulses. Binary transformations of each score returned from these test procedures will be produced. The dichotomization cutpoint will be a decrement in performance (or increase in difficulty) greater than the 75th percentile of the HRV's baseline responses. A multilevel binary logistic regression model, similar to that used to identify correlates of TTS, will be fitted to the data. The key difference is that the predictor variables will be the type of variable (e.g., tinnitus masking level, tone threshold in noise, ABR Wave I amplitude), which facilitates the evaluation of the relative odds and marginal probabilities of changes across outcome domains. Post-hoc comparisons, applying Bonferroni adjustment, will be used to determine whether one outcome domain is more likely to exhibit a change than another as a function of stimulus class, impulse energy level, and repetition number.

Data Management and Security

Management of Data

Data collection will occur during the eligibility determination visit, the arrival test series, the dose administration series bracketed by a daily test series and concluding with the departure test series. For all phases of data collection, the data acquisition and storage process will be governed by custom-written MATLAB® execution scripts. Even in cases when hardware-

specific software is needed to perform data collection, software will be spawned from within a MATLAB® shell to automate the data collection sequence as much as possible and ensure appropriate file naming and collection of associated metadata.

Table 7 provides a summary of the different types of data collection, file types, and estimated data volume associated with the eligibility determination visit. HRVs will complete a questionnaire, undergo video-otoscopy of each ear, participate in a clinical middle ear assessment battery, and testing of hearing sensitivity. The total data volume associated with each HRV enrollment is estimated to be approximately 500 MB. Assuming a 50 % attrition rate between initial enrollment and full data collection ($N = 500$), total data storage needs for the enrollment process will be approximately 1 terabyte (TB). The raw data storage format varies across specific test type.

Table 7. File Type and Estimated File Size for all Data Collection Procedures included in the Eligibility Determination Visit

Data Collection Procedure	File Type	Estimated File Size (MB)
Demographics and Hearing History Questionnaire	.PDF (scanning of paper) .MTB (MS Access)	2
Video-otoscopy	.AVI	500
Middle Ear Assessment	.XML	4
Hearing Sensitivity	.XLSX	1
Miscellaneous (e.g., calibration)	n/a	2
Data Volume per HRV		509

HRVs who meet the eligibility criteria will move onto the main experiment which includes the dose administration series. HRVs will be provided with a durable, long-term use wristband for the duration of their voluntary participation in the study. The wristband will include a linear bar code hearing research volunteer ID (HRVID) that will be scanned prior to each test procedure and saved to each data file, linking HRV data to the correct HRVID. The wristband will be removed and destroyed upon voluntary completion in the study. No electronic data will be linked to PII.

Table 8 is a summary of the associated data collection procedures, file types and estimated data volume. The main experiment includes the arrival test series, the dose administration series and the departure test series. All three data collection phases include the daily test protocol, which is a series of hearing and hearing-related tests. The shaded part of Table 4 includes details of all tests, file types and estimated data volumes associated with individual tests. A single run of the daily test procedure is estimated to require approximately 1.7 GB of data storage. The arrival test series and departure test series are identical and include a test run will be repeated twice per day on three consecutive days. Total data volume for a single test run is estimated to be 2 GB, resulting in a total data volume of 24 GB per HRV (2 tests per day for three days for each of the arrival and departure test series). The dose administration series requires up to five days of data collection in which each consecutive day involves an escalation in the impulsive noise exposure dose. Each daily dose administration series begins with a daily

test protocol, followed by the dose administration, immediate threshold testing and, finally, another daily test protocol. Average data volume for each HRV dose administration (including immediate threshold testing) is approximately 3 GB. That, combined with the two daily test protocols, will require approximately 7 GB of data per dose administration series. Assuming the HRV is subject to all five days of dose administration, there will be approximately 35 GB of data volume per HRV. The total data volume for all three phases is approximately 59 GB. Assuming 600 HRVs and an estimated 1 TB of data storage needs for acquisition of data related to controlling the exposures experiment, a total of 36 TB of data storage is required for the main experiment.

Table 8. File Type and Estimated File Size for all Data Collection Procedures at Exam and Field Sites.

Task	Raw Data File Type	Est. File Size (MB)
Daily Test Protocol		
Daily Questions	.PDF	1
Standing Balance	.PDF	1
Otoscopy: both ears	.AVI	500
Middle Ear Assessment	.XML	3
Hearing Sensitivity	.XLSX	1
Tinnitus Masking	.MAT	2
Thresholds in Noise	.MAT	2
Frequency Modulation Threshold	.MAT	2
Evoked Response Testing	.MAT	1172
Daily Test Protocol Total		1684
Arrival Test Series		
Daily Test Protocol		1684
DANA Neurocognitive Test	.CSV .MAT	2
HPD Fit Test	.MAT	1
High Frequency Hearing Sensitivity	.XLSX	2
MOC Reflex	.MAT	5
Airpuff Startle	.MAT	339
Ear canal dimensions	.STL	2
Arrival Test Series Total per test		2035
2 tests per day across 3 days		12210
Dose Administration Series		
Daily Test Protocol		1684
Abbreviated DANA test	.CSV .MAT	1
Small Arms Exposure	.MAT	3000
Immediate Testing	.XLSX	1
Abbreviated DANA test	.CSV .MAT	1

Daily Test Protocol		1684
Exposure Series Total		6371
One test per day across 5 days		31855
Departure Test Series		
Daily Test Protocol		1684
DANA Neurocognitive Test	.CSV .MAT	2
HPD Fit Test	.MAT	1
High Frequency Hearing Sensitivity	.XLSX	2
MOCR	.MAT	5
Airpuff Startle	.MAT	339
Departure Test Series Total per test		2035
2 tests per day across 3 days		12210
Data Collection associated with Control of Exposure Series	.MAT	500

Standard file formats will be used to store all raw data including MATLAB® (.MAT, version 7.3), extensible markup language (.XML), comma-separated values files (.CSV) Microsoft Excel® (.XLSX) and audio video interleave (.AVI) formats. Scans of ear canal geometry will use a standard stereolithography (.STL) format. Data related to demographic and hearing health history will be scanned as a portable document format (.PDF). Although the MATLAB®, Excel® and .XML data formats are expected to persist, all raw data files will be exported to .CSV format with column headers upon completion of data collection to ensure perpetual accessibility. The preferred format for saving any processed data will be MATLAB® (.MAT) format or Microsoft Access® (.MTB) for any questionnaire data. Summary data will be stored in STATA® (.DTA).

Four HRVs will be simultaneously tested during each dose administration series. Data collection from HRVs during impulsive noise exposures will be managed in the MATLAB® software environment, which will control multiple National Instruments (NI) hardware modules, including four PXIe-4499 16-channel modules and one PXIe-4461 output module. One 16-channel module is dedicated to each of the four HRV's data collection. Acquisition channels will include field recordings of sound exposure, ear canal recordings, surface recordings of head and neck muscle activity and physiological measures of arousal. An additional PXIe-6221 16-channel module will be used to collect data related to control of the experiment. All data will be acquired at a 200 kHz (24-bit) sample frequency to allow for accurate recording of the impulsive noise exposures.

Hardware parameters will be consistent with the most current draft of the revision of the ANSI S12.7 (impulse noise measurement) standard at the time the project begins. Acquisition software for acoustic signals will be configured for synchronous sampling across modules, with the post-hoc capacity to restore time-aligned signals in the event of synchronization failure. Data acquisition modules will be housed within an NI PXIe chassis (e.g., PXIe-1082) using a Thunderbolt 3 interface (PXIe-8301) for connection to a PC workstation running a Microsoft

Windows® 10 operating system. The PXIe-8301 interface supports a 2 GB/s bandwidth, which is sufficient for ongoing data transfer to the workstation.

Raw data files for each exposure series will be stored within MATLAB® STRUCTURE variables, which permit a hierarchical data structure. The raw data file will include all channels of all 4 HRVs, as well as the experimental control data. Immediately following acquisition, the single STRUCTURE will be automatically parsed into separate HRV files. HRV file names will be assigned with a numeric code to denote the HRV's identifier followed by numeric codes to indicate the order and type of the dose administration series. The file name will also include a suffix indicating the level of data review for the file and will be included in the file, with R0 indicating raw data. For example, the code "W216_4_33_R0" would indicate raw data from HRVID "W216" during the 4th dose administration series of 33 shots. The STRUCTURE will include a Date/time number returned by the MATLAB® NOW function immediately prior to initiating the data save. This function returns the current date and time where values to the left of the decimal represent the number of whole days since the beginning of the conventional calendar. For example, February 7, 2020 began 737,828 days after the start of the calendar. Decimal values represent the proportion of the day that elapsed since the start of the day (i.e., 0.5 is noon). The NOW function returns a value with 16-bit accuracy, which is unnecessarily precise; so, the middle section of each file name will include a 9-digit numerical value that embeds the time that the data was written to disk originally. If needed, additional versions of the file will increment the Review level (e.g., R2, R3, etc.). Reviews will be driven by custom MATLAB® functions written for this project.

Documentation and Metadata

Data files will be stored as MATLAB® structures. This data format permits a hierarchical data structure that can include a variety of data types, making it ideal for inclusion of metadata. Metadata within the structure will include, but is not limited to, HRVID, date and time stamps associated with data collection, details regarding the experimental condition (e.g. arrival series, day 1, test 1 or dose administration series 4, 33 stimuli), and information regarding any data collection protocol anomalies.

Although we consider the comprehensive Directory Interchange Format (DIF 10, <https://gcmd.nasa.gov/DocumentBuilder/defaultDif10/guide/index.html>) metadata standards beyond the scope of the information necessary for this project, some DIF fields will be used, including:

- Entry ID
- Entry Title
- Science Keywords
- Organization
- Summary
- Platform/Instruments
- Temporal Coverage
- Spatial Coverage
- Project

- Personnel
- Data Resolution
- Access Constraints
- Use Constraints
- Distribution
- Data Set Progress
- Originating Center
- DIF Revision History
- Privacy Status

Ethical and Legal Compliance

All data will be owned by USAARL. SASRAC will collect and analyze the data, and retain copies of the data on storage systems accessible only through Federal Information Processing Standards (FIPS) compliant security levels as determined by USAARL. SASRAC shall destroy data in their possession within 30 days of direction by USAARL to do so. Licensure/access of data to entities beyond USAARL and SASRAC will be granted at USAARL discretion and existing regulations upon request. Ownership of intellectual property associated with data processing algorithms, etc. that were developed by SASRAC will be owned by SASRAC with the understanding that USAARL has permanent license for modification and use of the property. Data will be transferred by hand to USAARL and SASRAC will use methods sanctioned by USAARL IT staff at the time of transfer.

Storage and Backup

Data will be stored on four identical NAS RAID systems (Synology RS2818RP+) each of which having 112 TB capacity including two failover drives and redundant power supplies. These drives will be distributed in multiple geographic areas (field site, exam site, SASRAC Oregon, SASRAC Ohio) and the nearest NAS will be accessed at each site using hardware firewall, intrusion prevention service, encryption, and VPN compliant with FIPS 140-2 (e.g., Watchguard Firebox M470). Data will be copied to the SASRAC RAID arrays for data management, processing, and synchronization across sites. In the event of a catastrophic failure not managed by the failover drives and redundant power supplies from an individual NAS, data will be restored from all but one of the duplicate RAID arrays accessible through the hardware VPN tunnel. In this event, one of the duplicate RAID arrays will be taken offline until the other systems have been re-synchronized to preserve the data stored in that system.

Controlled access to these data will be managed using smartcard authentication. Encrypted hardware-based VPN connections are used by personnel needing to access data from dedicated remote sites.

Selection and Preservation

Results from the present study will be made available via technical reports and publications. Following the completion of analyses, the reviewed data and processing/analysis

code will be preserved in both MATLAB (.MAT and .M) formats and in .CSV files, which will be enduring. SASRAC shall destroy data in their possession within 30 days of direction to do so by USAARL. Data preservation/archiving by USAARL shall be determined in accordance with existing regulations and USAARL discretion.

Data Sharing

Sharing of data to entities beyond USAARL and SASRAC will be granted at USAARL discretion and existing regulations upon request. Decisions about criteria or restrictions for sharing are at the sole discretion of USAARL.

Scientific Advisory Committee

Prior to commencing the proposed study, Scientific Advisory Committee will be convened. The Committee will include 3-6 scientists with expertise in at least one of the following topic areas: impulse noise-induced hearing loss, DRCs, cochlear synaptopathy, health effects of blast injury, and/or dose escalation studies. The role of the Committee will be to provide ongoing review of the project from conception to completion. The Scientific Advisory Committee will meet with the key personnel on a biannual basis (Figure 1).

Discussion

The primary outcome of this study is to identify an impulsive noise DRC for small arms that will be used to guide the safe training of personnel, and inform design and acquisition of weapons, wearable technology, and proper protection when using hearing protection devices. Impulsive noise from small arms is a significant risk factor for auditory injury among military Service Members. In addition to the lifelong health impact on the Service member, hearing injury can interfere with communications, situational awareness and overall operational success. Numerous impulsive noise DRCs have been developed that predict the ANOR of a given impulsive stimulus before unacceptable risk of auditory injury occurs. However, for a given impulse stimulus, the ANOR varies widely across different DRCs creating the practical challenge of determining which one is correct. Selecting a DRC that is too permissive negatively impacts warfighter health and readiness, while a DRC that is overly restrictive limits flexibility in warfighter training, and effectiveness and lethality of future materiel acquisition. The military requires a resolution to this situation and the proposed study outlines a strategy. In short, this study will employ a dose-escalation procedure with HRVs to prospectively identify the DRC that provides the largest ANOR without exceeding the MTD (defined by a criterion TTS) across a range of exposure environments. Beyond the primary outcome, the study is also positioned to provide much-needed data relating factors such as gender, race/ethnicity, prior exposure, measures of so-called “cochlear synaptopathy,” and neurocognitive measures to the susceptibility of TTS and its resolution. Finally, the study design is sufficiently flexible to allow expansion to other exposure environments that potentially pose elevated risk for hearing and neurocognitive injury (e.g., large caliber weapons).

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Appendix 1. List of Abbreviations, Acronyms, and Symbols

ABR	Auditory Brainstem Response
ADL	Activities of Daily Living
AEP	Auditory Evoked Potentials
AHAAH	Auditory Hazard Assessment Algorithm for the Human
AHU U	Auditory Hazard Units - Unwarned
AHU W	Auditory Hazard Units - Warned
ANOR	Allowable Number of Rounds
BAC	Blood Alcohol Content
BDA	Blank Discharge Apparatus
BOP	Blast Overpressure
CMF	Career Management Field
CTCAEv5	U.S. National Cancer Institute Common Terminology for Adverse Events, v.5
DANA	Defense Automated Neurobehavioral Assessment
DAQ	Data Acquisition
dB	Decibels
DIF	Directory Interchange Format
DRCs	Damage Risk Criteria
ECochG	Electrocochleography
EMG	Electromyography
ER	Etymotic Research
FIPS	Federal Information Processing Standards
GB	Gigabyte
HL	Hearing Level
HPD	Hearing Protection Device
HRV	Human Research Volunteer
HRVID	Human Research Volunteer ID
HVAC	Heating, Ventilation and Air Conditioning
ICE NR	Integrated Cochlear Energy - No Reflex
ICE U	Integrated Cochlear Energy - Unwarned
IET	Initial Entry Training
kHz	Kilohertz
LAeq8	8 Hours Equivalent A-Weighted Energy
LIAeq8	8 Hours Equivalent A-Weighted Energy for Impulsive Noise
MAS	Masseter Muscle
MB	Megabyte
MEMC	Middle Ear Muscle Contraction
MOCR	Medial Olivocochlear Reflex
MOS	Military Occupational Specialty
MTD	Maximum Tolerable Dose
NAS	Network Attached Storage
NCO	Noncommissioned Officer

NHANES	National Health and Nutrition Examination Survey
NI	National Instruments
NSI	Neurobehavioral Symptom Inventory
OAE	Otoacoustic Emissions
OHC	Occupational Hearing Conservationist
OOC	Orbicularis Oculi Muscle
PC	Personal Computer
PII	Personal Identifying Information
PTS	Permanent Threshold Shift
RAID	Redundant Array of Independent Disks
SASRAC	Stephenson and Stephenson Research and Consulting
SCM	Sternocleidomastoid Muscle
SD	Standard Deviation
SPH	Suprahyoid Muscle Complex
SPL	Sound Pressure Level
TB	Terabyte
TDY	Temporary Duty Travel
TECHID	Technician Identification Number
THS	Tinnitus and Hearing Survey
TTS	Temporary Threshold Shift
USAARL	U.S. Army Aeromedical Research Laboratory
VIC	Voluntary Informed Consent
VPN	Virtual Private Network

Appendix 2. Arrival Questionnaire

INSTRUCTIONS

We want to know how your ears feel today and about anything that may have changed recently that might affect your eligibility to participate in this study.

To answer each question, please read each item carefully and mark the box below the phrase that best describes your answer.

Some questions lead to other follow-up questions marked with an "a" or "b". Please respond to these questions also.

Please begin answering questions here

Please read the statements below.

1. I am willing to participate in a study requiring full-time TDY to the study site for 16 days and up to 20 days.
2. I have successfully completed Initial Entry Training (IET).
3. I have not been issued a medical waiver or assignment limitation during my time in the military.
4. I have qualified or re-qualified with a military weapon within the past 24 months.
5. I am eligible to handle an unloaded M4 carbine.
6. I have never taken medications that affected my hearing (ototoxic medications).
7. I have never taken antibiotics that were injected into my bloodstream (IV antibiotics).
8. I have never had surgery of the ear or bone surrounding the ear (temporal bone, mastoid).
9. I do not have a history of skin allergies or sensitivity to cosmetics, location, or alcohol-based hand sanitizers.
10. I am not pregnant. (If there is a possibility you could be pregnant, we strongly encourage you to visit the clinic to get tested.)
11. I have not experienced ringing or other noises in my ears that was bothersome enough to interfere with my concentration or ability to sleep.
12. I am not currently taking any prescription medications (except birth control).
13. I am not currently participating in other research studies.

If all of these statements are true, please mark "yes". If one or more statements are not true, please mark "no". Please do not indicate which statements are not true.

no	yes
☐	☐

1. **Are you feeling any dizziness or lightheadedness now?**

no	yes
☐	☐

IF YES:

- a. How much of a problem is this dizziness or lightheadedness?**

no problem	small problem	moderate problem	big problem	very big problem
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☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

2. **Do you now have pain in either of your ears?**

no	yes
☐	☐

3. **Do you now have ringing or other noises in your ears or head?**

no	yes
☐	☐

IF YES: Please answer the following questions about tinnitus (noises in the ear or head) and hearing. Circle the number that most closely matches how much of a problem each sentence is. For example, circling 0 means "No, not a problem."

	No, not a problem	Yes, a small problem	Yes, a moderate problem	Yes, a big problem	Yes, a very big problem
A. Tinnitus					
A.1 Over the last week, tinnitus kept me from sleeping.	0	1	2	3	4
A.2 Over the last week, tinnitus kept me from concentrating on reading.	0	1	2	3	4
A.3 Over the last week, tinnitus kept me from relaxing.	0	1	2	3	4
A.4 Over the last week, I couldn't get my mind off of my tinnitus.	0	1	2	3	4
B. Hearing					
B.1 Over the last week, I couldn't understand what others were saying in noisy or crowded places.	0	1	2	3	4
B.2 Over the last week, I couldn't understand what people were saying on TV or in movies.	0	1	2	3	4
B.3 Over the last week, I couldn't understand people with soft voices.	0	1	2	3	4
B.4 Over the last week, I couldn't understand what was being said in group conversations.	0	1	2	3	4
C. Sound Tolerance					
C.1 Over the last week, sounds were too loud or uncomfortable for me when they seemed normal to others around me.	0	1	2	3	4

If you responded 1, 2, 3, or 5 to the statement above, please list two examples of sounds that were too loud or uncomfortable for you, but seem normal to others:	C.2.1.	
	C.2.2.	

Appendix 3. Demographic and History Questionnaire

Demographic and History questions

Instructions:

We want to know a little about your background and some of the things you do currently. Please respond to each of the numbered questions. Depending on your answers to these questions, we might have some

1. What is your age in years? (For example: 21 years old)

_____ years old
2. Are you male or female?
 - ☐ Male
 - ☐ Female
 - ☐ Do not wish to provide
3. Is there any possibility you could be pregnant? If yes, we strongly encourage you to visit the clinic to get tested.
 - ☐ Yes
 - ☐ No or does not apply
4. What are the first two characters of your military occupation specialty (MOS)? For example, Infantry Branch = MOS 11.

5. What is the highest grade or level of school you have completed or the highest degree you have received?

6. In your current or most recent job prior to enlisting in the military, what kind of work did you do? (For example: farming, mail clerk, computer specialist)

7. Please look at the race and ethnicity categories below. Which do you consider yourself to be?
 - ☐ American Indian or Alaskan Native
 - ☐ Asian
 - ☐ Black or African American
 - ☐ Native Hawaiian or Pacific Islander
 - ☐ White
 - ☐ Don't know

☐ Do not wish to provide
PAGE

CONTINUE TO NEXT

8. Which statement best describes your hearing (without a hearing aid)? Would you say your hearing is excellent, good, that you have a little trouble, moderate trouble, or are deaf?

- ☐ Excellent
- ☐ Good
- ☐ A little trouble
- ☐ Moderate hearing trouble
- ☐ A lot of trouble
- ☐ Deaf

9. Have you ever had 3 or more ear infections?

- ☐ No
- ☐ Yes

10. Have you ever had a tube placed in your ear to drain the fluid from your ear?

- ☐ No
- ☐ Yes

11. When was the last time you had your hearing tested?

- ☐ Less than a year ago
- ☐ 1 year to 4 years ago
- ☐ 5 to 9 years ago
- ☐ 10 or more years ago
- ☐ Never

12. Have you ever had a seizure?

- ☐ No
- ☐ Yes

13. Have you ever experienced sudden weakness or paralysis on one side of your face that caused it to droop, numbness on your face, drooling, loss of ability to taste, pain in or behind your ear, or increased sensitivity to sound?

- ☐ No
- ☐ Yes ➡

i. Has a doctor ever told you that you have Bell's palsy?

- ☐ No
- ☐ Yes

CONTINUE TO NEXT PAGE

14. Have you ever experienced ringing or other noises in the ears or head that was caused or worsened by loud noise? (Examples: loud concert, firearms, fireworks)

☐ No

☐ Yes 

i. How many times has this happened?

☐ 1 to 4 times

☐ 5 to 9 times

☐ 10 to 24 times

☐ 25 to 74 times

☐ 75 or more times

ii. Think of the worst time this happened. How many years ago did it happen?

☐ Less than a year ago

☐ 1 year to 4 years ago

☐ 5 to 9 years ago

☐ 10 or more years ago

iii. What was the source of the loud noise?

iv. How much of a problem was the ringing or other noises in the ears or head after the loud noise?

☐ Not a problem

☐ A small problem

☐ A moderate problem

☐ A big problem

☐ A very big problem

v. How long did the ringing or other loud noises in the ears or head that was caused or worsened by the loud noise last?

☐ Less than 5 minutes

☐ 5 minutes to 1 day

☐ 1 day to 1 week

☐ 1 week to 1 month

☐ 1 month to 6 months

☐ More than 6 months

☐ I still have ringing or other loud noises in my ears or head caused by the loud noise

CONTINUE TO NEXT PAGE

15. Have you ever experienced a temporary decrease in hearing that was caused by loud noise? (Examples: loud concert, firearms, fireworks)

☐ No

☐ Yes ➡

i. How many times has this happened?

☐ 1 to 4 times

☐ 5 to 9 times

☐ 10 to 24 times

☐ 25 to 74 times

☐ 75 or more times

ii. Think of the worst time this happened. How many years ago did it happen?

☐ Less than a year ago

☐ 1 year to 4 years ago

☐ 5 to 9 years ago

☐ 10 or more years ago

iii. What was the source of this loud noise?

iv. How much of a problem was the temporary decrease in hearing after the loud noise?

☐ Not a problem

☐ A small problem

☐ A moderate problem

☐ A big problem

☐ A very big problem

v. How long did the decrease in hearing last after the loud noise?

☐ Less than 5 minutes

☐ 5 minutes to 1 day

☐ 1 day to 1 week

☐ 1 week to 1 month

☐ 1 month to 6 months

☐ More than 6 months

☐ I still have decreased hearing caused by the loud noise

CONTINUE TO NEXT PAGE

16. Have you ever been on any of the following medications? Please select any that apply.

- ☐ Gentamicin
- ☐ Tobramycin
- ☐ Amikacin
- ☐ Streptomycin
- ☐ Cisplatin
- ☐ Carboplatin
- ☐ Quinine (Qualaquin)
- ☐ Bumetanide (Bumex)
- ☐ Furosemide (Lasix)
- ☐ Torsemide (Demadex)
- ☐ Telavancin (Vibativ)
- ☐ Vancomycin
- ☐ Any cancer chemotherapy medication
- ☐ None of the above or don't know

17. Do you sometimes feel dizzy or lightheaded?

☐ No

☐ Yes ➡

i. Have you ever seen a doctor to determine the cause of your dizziness or lightheadedness?

☐ No

☐ Yes ➡

a. Has a doctor ever diagnosed the cause of the dizziness or lightheadedness?

☐ No

☐ Yes, please explain _____

b. Has a doctor ever told you that you have unexplained dizziness?

☐ No

☐ Yes

CONTINUE TO NEXT PAGE

18. Have you ever hit your head so hard that it caused a loss of consciousness, headache, nausea or vomiting, tiredness, difficulty sleeping or more sleep than usual, dizziness, confusion, loss of memory, slurred speech, or ringing in the ears?

☐ No

☐ Yes ➡

i. Has a doctor ever told you that you have a concussion or a traumatic brain injury?

☐ No

☐ Yes ➡

a. Have you ever had symptoms from a concussion or traumatic brain injury that lasted for more than one month?

i. No

ii. Yes

b. How many times has a doctor told you that you have had a concussion or traumatic brain injury?

i. 1 time

ii. 2 times

iii. More than 2 times

CONTINUE TO NEXT PAGE

19. Have you smoked at least 100 cigarettes in your entire life?

☐ No

☐ Yes ➡

i. Do you now smoke cigarettes?

☐ Not at all ➡

a. How long has it been since you quit smoking cigarettes?

_____ months or years (circle one)

b. At that time, about how many cigarettes did you **usually** smoke per day?

_____ Cigarettes per day

☐ Some days ➡

a. On average, how many cigarettes do you **now** smoke per day?

_____ cigarettes

b. For about how many years have you smoked this amount?

_____ years

☐ Every day ➡

a. How soon after you wake up do you smoke your first cigarette?

☐ < 5 min

☐ 6 – 30 min

☐ 31 – 60 min

☐ 60 min

b. On average, how many cigarettes do you **now** smoke per day?

_____ cigarettes

c. For about how many years have you smoked this amount?

_____ years

END OF QUESTIONS. THANK YOU FOR YOUR RESPONSES.

Appendix 4. Noise and Solvent Exposure Questionnaire (LENS-Q)

See Bramhall, Konrad-Martin, McMillan, and Griest (2017).

Appendix 5. Tinnitus/Hearing Questionnaire-Eligibility Determination Visit

Please answer the following questions about tinnitus (ringing or other noises in the ear or head) and hearing. Circle the number that most closely matches how much of a problem each sentence is. For example, circling 0 means “No, not a problem.”

	No, not a problem	Yes, a small problem	Yes, a moderate problem	Yes, a big problem	Yes, a very big problem
A. Tinnitus					
A.1 Over the last week, tinnitus kept me from sleeping.	0	1	2	3	4
A.2 Over the last week, tinnitus kept me from concentrating on reading.	0	1	2	3	4
A.3 Over the last week, tinnitus kept me from relaxing.	0	1	2	3	4
A.4 Over the last week, I couldn't get my mind off of my tinnitus.	0	1	2	3	4
B. Hearing					
B.1 Over the last week, I couldn't understand what others were saying in noisy or crowded places.	0	1	2	3	4
B.2 Over the last week, I couldn't understand what people were saying on TV or in movies.	0	1	2	3	4
B.3 Over the last week, I couldn't understand people with soft voices.	0	1	2	3	4
B.4 Over the last week, I couldn't understand what was being said in group conversations.	0	1	2	3	4
C. Sound Tolerance					
C.1 Over the last week, sounds were too loud or uncomfortable for me when they seemed normal to others around me.	0	1	2	3	4
If you responded 1, 2, 3, or 5 to the statement above, please list two examples of sounds that were too loud or uncomfortable for you, but seem normal to others:	C.2.1.				
	C.2.2.				

Appendix 6. Modified Neurobehavioral Symptoms Inventory–Eligibility Determination Visit

Neurobehavioral Symptom Inventory (NSI) Eligibility Visit					
Please rate the following symptoms with regard to how much they have disturbed you IN THE LAST 2 WEEKS. The purpose of this inventory is to track symptoms over time. Please do not attempt to score. 0 = None – Rarely if ever present; not a problem at all 1 = Mild – Occasionally present, but it does not disrupt my activities; I can usually continue what I’m doing; doesn’t really concern me. 2 = Moderate – Often present, occasionally disrupts my activities; I can usually continue what I’m doing with some effort; I feel somewhat concerned. 3 = Severe – Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel I need help. 4 = Very Severe – Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.					
Symptoms	0	1	2	3	4
Feeling Dizzy	0	1	2	3	4
Loss of balance	0	1	2	3	4
Poor coordination, clumsy	0	1	2	3	4
Headaches	0	1	2	3	4
Nausea	0	1	2	3	4
Vision problems, blurring, trouble seeing	0	1	2	3	4
Sensitivity to light	0	1	2	3	4
Numbness or tingling on parts of my body	0	1	2	3	4
Change in taste and/or smell	0	1	2	3	4
Loss of appetite or increased appetite	0	1	2	3	4
Poor concentration, can’t pay attention, easily distracted	0	1	2	3	4
Forgetfulness, can’t remember things	0	1	2	3	4
Difficulty making decisions	0	1	2	3	4
Slowed thinking, difficulty getting organized, can’t finish things	0	1	2	3	4
Fatigue, loss of energy, getting tired easily	0	1	2	3	4
Difficulty falling or staying asleep	0	1	2	3	4

Appendix 7. Daily Questionnaire

Daily questions

Please begin answering questions here

1. **Have you had any health problems since your last visit?**

no	yes
☐	☐

IF YES, please describe them:

2. **Have you noticed any change in your hearing since your last hearing test?**

better	no change	worse	don't know
☐	☐	☐	☐

3. **Are you feeling any dizziness or lightheadedness now?**

no	yes
☐	☐

IF YES:

- a. How much of a problem is this dizziness or lightheadedness?**

no problem	small problem	moderate problem	big problem	very big problem
☐	☐	☐	☐	☐

4. **Do you now have pain in either of your ears?**

no	yes
☐	☐

5. **How long has it been since you last smoked a cigarette?**

Less than 30 min	30 min to 1 hr	1 – 2 hours	2 – 4 hours	4 – 24 hours	Over 24 hours or never
☐	☐	☐	☐	☐	☐

6. **Have you listened to music or other sound through earphones since your last visit?**

no	yes
☐	☐

IF YES:**a. In total, how much time did you spend listening to music through earphones since your last visit?**

Less than 15 min	15 – 30 min	30 min to 1 hour	1 – 2 hours	2 –4 hours	Over 4 hours
☐	☐	☐	☐	☐	☐

b. On average, how high was the volume on the music player?

$\frac{1}{4}$ of the way up	$\frac{1}{2}$ of the way up	$\frac{3}{4}$ of the way up	All the way up
☐	☐	☐	☐

Please rate the following symptoms with regard to how much they have disturbed you SINCE YOUR LAST VISIT. The purpose of this inventory is to track symptoms over time. Please do not attempt to score.

0 = None – Rarely if ever present; not a problem at all

1 = Mild – Occasionally present, but it does not disrupt my activities; I can usually continue what I’m doing; doesn’t really concern me.

2 = Moderate – Often present, occasionally disrupts my activities; I can usually continue what I’m doing with some effort; I feel somewhat concerned.

3 = Severe – Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel I need help.

4 = Very Severe – Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.

7. Symptoms					
7a. Feeling Dizzy	0	1	2	3	4
7b. Loss of balance	0	1	2	3	4
7c. Poor coordination, clumsy	0	1	2	3	4
7d. Headaches	0	1	2	3	4
7e. Nausea	0	1	2	3	4
7f. Vision problems, blurring, trouble seeing	0	1	2	3	4
7g. Sensitivity to light	0	1	2	3	4

8. Do you now have ringing or other noises in your ears or head?

no	yes
☐	☐

IF YES: Please answer the following questions about tinnitus (noises in the ear or head) and hearing. Circle the number that most closely matches how much of a problem each sentence is. For example, circling 0 means "No, not a problem".

	No, not a problem	Yes, a small problem	Yes, a moderate problem	Yes, a big problem	Yes, a very big problem
A. Tinnitus					
A.1 Over the last week, tinnitus kept me from sleeping.	0	1	2	3	4
A.2 Over the last week, tinnitus kept me from concentrating on reading.	0	1	2	3	4
A.3 Over the last week, tinnitus kept me from relaxing.	0	1	2	3	4
A.4 Over the last week, I couldn't get my mind off of my tinnitus.	0	1	2	3	4
B. Hearing					
B.1 Over the last week, I couldn't understand what others were saying in noisy or crowded places.	0	1	2	3	4
B.2 Over the last week, I couldn't understand what people were saying on TV or in movies.	0	1	2	3	4
B.3 Over the last week, I couldn't understand people with soft voices.	0	1	2	3	4
B.4 Over the last week, I couldn't understand what was being said in group conversations.	0	1	2	3	4
C. Sound Tolerance					
C.1 Over the last week, sounds were too loud or uncomfortable for me when they seemed normal to others around me.	0	1	2	3	4
If you responded 1, 2, 3, or 4 to the statement above, please list two examples of sounds that were too loud or uncomfortable for you, but seem normal to others:	C.2.1.				
	C.2.2.				

U.S. Army Aeromedical Research Laboratory Fort Rucker, Alabama

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