

VA Office of Research and Development Results Record C0239-R

Title: Randomized Trial Comparison of Ototoxicity Monitoring Programs

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Experimental Methods

A. Subjects.

A1. Subject Recruitment: An estimated 320 patients from VA Portland Health Care System (VAPORHCS) receiving chemotherapy will be identified by a search of the upcoming chemotherapy unit appointment list, pharmacy list or by oncology referral including verbal referral and encrypted email. Additionally, approximately 120 healthy control subjects (Veterans and non-Veterans) not administered chemotherapy will also be recruited at the VAPORHCS from posted recruitment advertisements and from the NCRAR database of Veterans willing to participate in future hearing research projects. Potential chemotherapy patients will be accessed using electronic medical records (CPRS) to determine the diagnosis and treatment plan and to search for exclusionary criteria. If the potential subject is not excluded based on initial CPRS search, oncology personnel will approach the potential subject to determine his/her willingness to learn more about the study after hearing a brief description. The Program Evaluation (PE) audiologist will then talk with the patient, offer a more thorough explanation of the study, including the necessity for duplicate testing. If the potential subject remains interested in the project, informed consent will be obtained including an explanation of the goals of the study, requirements of the study protocol and the potential risks and benefits to the subject.

Initial testing to establish inclusion in the study and to provide the first PE will be done in a quiet area. After the evaluation, if the subject has met all further inclusion criteria, the subject will be randomized to a treatment arm: Standard of care (SOC) or Comprehensive Ototoxicity Monitoring Program for VA healthcare (COMP-VA). Study personnel will then be informed that a subject has been consented, tested, and assigned to a study arm and is ready to receive a baseline evaluation.

A2. Subject Exclusion Criteria: Subjects must be treated for cancer and must provide a reliable hearing test to be enrolled in the treatment arms of this study. Criteria for excluding subjects (chemotherapy and controls subjects) from this study are: 1) cognitively or physically unable to participate (patient or nurse report patient is incapable of participating), CPRS indication that subject exhibits aggressive behavior, subject has documented dementia, Alzheimer's disease, or severe psychosocial disorder, CPRS notes indicate individual is not legally capable of providing informed consent (subject has a legal guardian); 2) exhibits Meniere's disease or retrocochlear disorder based on hearing test results, patient report or notes in CPRS; 3) exhibits active or recent history of middle ear disorder based on otoscopy, tympanometry, patient report, or notes in CPRS; 4) unwilling to participate; and 6) hearing thresholds > 70 dB SPL at 4 kHz and below (control subjects only).

B. Experimental Techniques. Study measurements are divided into three general groups: Program Evaluation measurements, SOC measurements (Arm 1) and COMP-VA measurements (Arm 2). Measurements in non-clinical controls generally mirror those done for the COMP-VA arm. Testing is done by an Audiologist. The SOC protocol (Arm 1: SOC) is done according to the Audiology Service established protocol. The COMP-VA (Arm 2) protocol includes hearing testing at baseline and at each treatment interval along with a one-month post-treatment evaluation. Testing will be done using OtoID and/or the OtoID-Tablet and/or a standard audiometer. As part of this project, we have developed an updated version of the OtoID which involved migrating to a tablet-controlled device. Like all audiometers, this audiometer is not a medical device since it is "non-invasive" and, therefore, does not require FDA oversight or approval. Rather, the OtoID-Tablet properties are defined and calibrated according to the American National Standards Institute (ANSI) S3.6-2010 "Specification for Audiometers". It was calibrated in 2017 and will be calibrated annually, per ANSI standards.

B1. PE and Longitudinal Follow-up Measurement: Program Evaluations will be completed in a quiet area and include 1) otoscopy; 2) tympanometry; and 3) hearing threshold testing and 4) the audiologist can elect to include DPOAE testing at any session. Various questionnaires will be given at the discretion of the audiologist. A study team member may request a patient's feedback in the form of a set of mostly open ended questions (Patient Interview Form). A phone call from PE study personnel will be made at regular intervals to inquire about the subject's general well-being, to determine if the

Veteran has experienced any recent noise exposure and retains adequate hearing protection, to ensure that contact information is accurate and not likely to change in the near future, and to remind the Veteran that study personnel will require a final hearing testing session (PE #3). The Veteran may be asked if he/she received any audiological care since the previous contact and requested to bring a report from this contact to the final (longitudinal) program evaluation. Subjects consented and tested may receive a longitudinal follow-up program evaluation depending on their randomization date.

B2. General Procedures for Ototoxicity Monitoring: Attempts will be made to establish baseline results within approximately 24 hrs of treatment. Results from the baseline test will be compared to all subsequent testing for the purposes of ototoxicity detection. Subjects will be provided with education about their hearing, potential changes in hearing and tinnitus associated with ototoxicity and the increased vulnerability of their auditory system to excessive noise exposure for at least a 1-year period after treatment. Disposable-type hearing protection is readily available to subjects at the VA Audiology Clinic and NCRAR.

B2a. Monitoring Procedures for Standard of Care (SOC): Hearing testing will be done according to their established protocol for ototoxicity monitoring in the Audiology Clinic.

B2b. Monitoring Procedures COMP-VA: COMP-VA hearing testing is done primarily using the OtoID and/or the OtoID-Tablet and/or a standard audiometer. *Baseline and monitor* testing may include: 1) otoscopy; 2) tympanometry; 3) pure tone air-conduction threshold testing; 4) DPOAE testing and 5) questionnaires. If the test results suggest a hearing change or that the Veteran is unable to complete the self-test, the subject may complete additional testing. Results will be entered into a CPRS progress note. A verified hearing change will be reported with oncology medical staff. Approximately one month after treatment ceases, subjects will be evaluated using procedures described above. The questionnaires may be given at each visit.

B3a. DPOAE measures for SOC: DPOAE measurements will be done according to their ototoxicity monitoring protocol.

B3b. DPOAE measures for COMP-VA: Testing will be done by study personnel in a quiet area.

B3b1. Baseline measurements COMP-VA: This testing may be done following the hearing test. Further testing is reserved primarily for those instances when the patient cannot take a reliable hearing test though the audiologist may elect to include DPOAE testing when time permits.

B4. DPOAE Reference Limits Testing on non-Clinical Control Subjects: 120 healthy control subjects will have their hearing and DPOAEs measured serially. Subjects must meet all established exclusionary criteria. Subjects will be tested approximately 6 times over the course of about 3 to 6 months. The variability in the numbers of tests and time frame is to allow our testing regimen to mimic several different cancer therapy regimens. In addition to DPOAE testing, protocol includes: Otoscopy, tympanometry, and hearing testing. Testing of control subjects will be done in a quiet area.

C. Instrumentation.

C1. Behavioral Testing Instrumentation for SOC: Equipment and space used for testing at the VAPORHCS Audiology clinic will be used for SOC. Equipment undergoes full calibration annually.

C1a. Behavioral Testing Instrumentation for COMP-VA: The OtoID audiometers (OtoID and OtoID-Tablet) are calibrated annually with level checks done at least monthly.

C2. Distortion Product Otoacoustic Emission Instrumentation for SOC: Distortion-product otoacoustic emission testing is currently accomplished using commercially-available equipment.

C2a. Distortion Product Otoacoustic Emission Instrumentation for COMP-VA: Either the OtoID-based DPOAE testing (or cart system) can be used to collect DPOAEs.

C3. Other data to be gathered on study participants with cancer: Additional information obtained on each subject from the electronic medical records (CPRS) will be entered into the database, maintained by by study team members including a biostatistician and research assistant(s). Information to be obtained will include patient factors such as name, gender, age, type of cancer and staging, drug treatment variables such as cisplatin dose and dosing (intensity) and concomitant radiation dose and doublet medication and other information related to treatment and patient factors as required to accomplish the study goals. CPRS clinical progress notes will be monitored by a study team member on each subject (estimated n=80/yr) entered into either study arm in order to obtain Audiology Service utilization **for up to one year** post-randomization. In addition, in order to get a less biased estimate of audiological services utilization rates, an historical cohort comprised of all patients identified as receiving cisplatin approximately 3 years prior to the initiation of the study will be searched in CPRS and the cancer registry for audiological services used (estimated n=220 pts). We estimate approximately 300 patient records may be accessed to complete this search. These data may be combined with data from other studies done by these investigators in an IRB-approved manner.

A study team member may request providers' feedback in the form of a simple checklist (Oncology Practitioner Survey) provided to them at each treatment interval by a study team member.

We may also survey practitioners (oncologists, nurses, and audiologists) to assess their beliefs about ototoxicity monitoring practices using an anonymous beliefs questionnaire (i.e., no PHI or PII). This survey will be made available at 2 intervals.

In order to establish a benchmark for relapse-free survivorship from which to compare COMP-VA subjects' survivorship, we will be evaluated survivorship of Veterans with a diagnosis of cancers treated with cisplatin using the VA Cancer Registry (or other) which follows Veterans treated in VA for 5+ years following treatment. We will follow current study participants for cancer survivorship for approximately 2-3 years depending on enrollment date and resources available to do so.

D1. Reporting Methods: All study related data are confidential and will be kept in secured locations at the NCRAR, Chemotherapy Treatment Unit 6C of the hospital, and the Audiology Clinic using password protected computers, locked offices, and cabinets in locked offices. The oncology medical personnel will be notified verbally and/or via CPRS notes if behavioral hearing threshold shifts meet or exceed criterion levels. Communication with oncology may occur in 2 ways: oncology study personnel may be sent a secure encrypted and restricted Outlook email to view indicating the subject number and name of the subject in order to find previous testing stored in the OtoID. The subject number is important since the data (hearing test results) stored on the OtoID contains only de-identified information including subject numbers and no patient identifiers. In addition, a lock-box containing a copy of the key that links the study subject name and the study number may be stored on the Chemotherapy Unit in the medication room (Rm 6C-157). This medication room is locked at all times and is only accessible to oncology medical personnel. This lock box is password protected with only IRB-approved study team members given the code. The study personnel nurse will be instructed to delete any email after use. Electronically-stored data will be kept at: **S:NCRAR/DilleArchive/COMP-VA**, including the linking key between the PII and the data, all of which are password protected.

Once the study is completed, our intent is to bank all data collected under this approved study protocol if the subject allows (through written informed consent) the information collected to be added to a repository. This study will contribute samples to the "Data Repository for the Normal and Abnormal Functioning of the Auditory System, PI: Dawn Konrad-Martin MIRB# 3589" located at the VAPORHCS for future use. If the subject opts out of the data repository, hard copies of data including identifiable data will be kept per IRQ (11-26-14) in a locked cabinet in a locked room (**P5F-189**) at the NCRAR and/or in a locked desk in a locked room (**1D-116a**) the Audiology Clinic.

E. Early Exit: Exit from study will occur if the Veteran 1) moves and will not live within proximity to permit continued participation; 2) elects to withdraw from the study; 3) fails to meet study protocol requirements.