VA Office of Research and Development Results Record C0239-R

Title: Randomized Trial Comparison of Ototoxicity Monitoring Programs

ClinicalTrials.gov identifier: NCT02099786

Outcomes and Statistical Plan; Document Date: 9-29-17

Outcomes and Statistical Plan

Outcome Measures

The following outcomes were evaluated as a function of treatment arm.

1. **Hearing tests.** Rates of ototoxicity were evaluated using two criteria: (i) Ototoxic hearing shifts meeting the ASHA 1994 definition 20dB shift at one frequency; 10 dB shift at two consecutive frequencies or loss of response at three frequencies. (ii) Ototoxicity meeting the Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or greater toxicity [hearing shift of 15-25 dB averaged at 2 contiguous test frequencies in at least one ear.

2. **Audiology rehabilitation service use.** This included: (i) service utilization to issue new hearing aids to subjects who were not hearing aid users at baseline; and (ii) technology update or hearing aid adjustment for previous hearing aid users. CPRS progress notes were monitored by the NCRAR Research Audiologist on each subject enrolled in the study in order to determine audiology rehabilitation service use for one year post-randomization. All audiology clinic visits were recorded by date and type of visit. Additionally, subjects were queried about aural rehabilitation service at each PE and interim phone calls.

3. **Quality of life measures.** Differences in the HHIA questionnaire score (or HHIE score as appropriate depending on the age of the subject) at PE 3 were evaluated.

4. **Survivorship** among subjects was also evaluated, defined as differences in rates of death during the study period.

Hypotheses to be Tested and Statistical Plan

1. *Use of COMP-VA will improve patients' hearing and quality of life outcomes without diminishing chances for survival*. Simple analysis will entail computing odds ratios and contrasting these between the COMP-VA and SOC groups. We will also fit a logistic regression model to the probability of ototoxicity (separately modeled for ASHA and CTCAE grade 1 or

greater) with randomization group assignment as predictor. *We anticipate that hearing loss progression will be less among COMP-VA subjects, meaning that, the COMP-VA group will have smaller 35 day and 1 year post-randomization hearing shifts compared to SOC patients.*

2. *We hypothesize that COMP-VA will minimize some of the adverse effects of cisplatin treatment on Veterans' hearing-related quality of life, either through treatment modifications to diminish cisplatin-induced hearing loss or effective post-chemo audiological service delivery to limit the ill-effects of any pre-existing, new or worsened communication deficit.* We will conduct a contrast of perceived hearing handicap (HHIE or HHIA questionnaire administered at 1 year post-randomization), between patients randomized to COMP-VA and SOC. We will conduct a t-test with randomization arm as the contrast to test the importance of COMP-VA on perceived quality of life outcomes.

3. *Compared with patients randomized to SOC, patients randomized to COMP-VA will use Audiology rehabilitation services at a higher rate because of their greater awareness of new, increased or pre-existing communication deficits.* To test this hypothesis, we will contrast the probability of one or more audiology clinic rehabilitation visits using logistic regression with group membership as a factor.

4. *We anticipate that cisplatin patients given the COMP-VA intervention will fair no worse than SOC patients in terms of their survival.* This component of the study is framed as a non-inferiority trial. i.e. we require sufficient evidence to reject the null hypothesis that COMP-VA patients have lower one-year survival rates than patients treated under SOC. Analysis for non-inferiority trials using survival outcomes have been described and are easily computed using logistic regression output. We will require a non-inferiority margin of no more than 1.1 mortality odds among COMP-VA patients relative to SOC patients. From an analytical

perspective this means that the upper 95% confidence bound for the fitted odds ratio must

be less than 1.1 to reject the null hypothesis that COMP-VA induces extra mortality risks.