Study Title: **Evaluation of two mouth sprays for post-irradiation xerostomia in head and neck cancer survivors: a randomized, double-blind clinical trial**

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Objective(s):

The main objective of this study is to compare the efficacy of two FDA-approved mouth sprays (Biotene and Refresh) at relieving symptoms of xerostomia, or dry mouth, in patients who have received radiation for carcinoma of the head and neck. We aim to conduct a randomized, double-blinded, crossover study to demonstrate to what extent, two different FDA-approved mouth sprays are effective in relieving symptoms of xerostomia in patients who meet inclusion criteria for this study. We also want to determine to what extent, these mouth sprays are superior to water or to one another at relieving symptoms of xerostomia in this population. We will test the hypothesis that the use of either Biotene or Refresh mouth spray will be more effective at relieving symptoms of xerostomia than the use of water as mouth spray and that either Biotene or Refresh mouth spray will be more effective than the other at relieving symptoms of xerostomia in the included patients in this study. We also will test the hypothesis that both mouth sprays will increase the pH of patient mouths compared to water.

Study Design:

This 6-week study will consist of two experimental phases lasting two weeks each. Both phases will be preceded by one-week washout periods. Patients will be randomized to receive test treatments of either Refresh mouth spray or Biotene mouth spray during the first experimental phase. They will receive the opposite mouth spray during the second experimental phase. Patients will be given a 1-month supply of both masked mouth sprays labeled as "Oral Hydrating Spray A" and "Oral Hydrating Spray B", as well as pH testing strips, prior to the initiation of the study. They will be given specific directions regarding the usage of the mouth sprays. They may use the mouth sprays as needed, every four hours, with 4 sprays per use at the start of both respective experimental phases. Additionally, subjects will be asked to measure mouth pH values at scheduled timepoints. Patients will be permitted to use water as a mouth spray during washout periods. The use of chewing gum, hard candy, and lozenges will be prohibited for the duration of the study, but liquid intake will not be limited. Patients will complete an xerostomia and demographics questionnaires at specified timepoints during the conduct of the trial. Participants can use 4 sprays every 4 hours. However, the frequency of usage is symptoms dependent. If participants are still experiencing relief after 4 hours, they may delay the next usage.

Recruitment Methods:

Patients will be recruited, in person, from the Head and Neck Survivorship clinic at the University of Pittsburgh Medical Center (UPMC). Patients will be screened for

xerostomia at their regularly scheduled clinical visit and will be approached by clinical staff who are educated in this research to participate in this study if they meet participation criteria. For any patients other than those of Dr. Johnson's, a clinical care provider known to the patient will confirm that the potential subject has given permission for the research team to approach.

Stastical Analysis Plan:

All statistical analyses were performed using STATA SE 17.0 for Mac OS. Descriptive statistics, including proportions, means, medians, standard deviations (SD), and interquartile ranges (IQR), were used to compare demographic and clinical features between treatment groups. The primary outcomes were reported dry mouth scores derived from the 100-mm VAS. Washout period scores were used as the baseline comparison for the mouth spray period that directly followed. Carryover effect was tested by unpaired t-test of the sum of primary outcomes after both treatments, with sequence as the grouping variable.[9] Period effect was tested by unpaired t-test of the difference in primary outcomes between Biotène and HydraSmile after both treatments, with sequence as the grouping variable. To evaluate the treatment effect of Biotène and HydraSmile, we used paired t-test to compare the primary outcome after treatment compared to the corresponding baseline measurements. To investigate the treatment effect of HydraSmile vs Biotène, we followed the recent recommendation for analysis of 2*2 cross-over trials with two baseline measurements by Metcalfe and Mehrotra and implemented the analysis of covariance (ANCOVA) model to regress the difference in after-treatment measurement between HydraSmile and Biotène over the difference of baseline between HydraSmile and Biotène.[10,11] The intercept term would be the treatment effect of HydraSmile compared to Biotène. In the exit survey, patients indicated which mouth spray (Biotène or HydraSmile) they preferred. Sub-group analysis was completed within each preference group to determine the effect of each mouth spray and the difference between them.