A text-based reduction intervention for smokeless tobacco cessation

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Data Analysis Plan

We will use descriptive statistics to summarize the sample characteristics and study measures collected at baseline and longitudinally. We will perform non-directional statistical tests with the significance level set at 0.05 for all analyses. The primary outcome is self-report smokeless tobacco cessation at month 6 (Aims 1 & 3). Due to the exploratory nature of the mediator analyses, the significance level of 0.05 will not be adjusted for the multiple tests associated with steps for determining mediation (Aims 2 & 3). For the efficacy and mediator analyses we will perform, both intention-to-treat (ITT) and completers analyses. ITT analyses will be the primary analyses and will include all participants randomized to an intervention regardless of treatment or study completion. Completers analyses will include only those participants who complete the month 6 assessment, regardless of level of adherence to the SGR or control intervention. Effect sizes and 95% confidence intervals (CIs) will be reported to address clinical significance for the efficacy and mediator analyses. Analyses will be conducted by our faculty biostatistician Dr. Silva (Co-I) to ensure application of rigorous methods and implementation of quality assurance procedures. All data will be stored in REDCap at Duke University and downloaded to SAS Version 9.4 for the statistical analysis.

Handling of Missing Data. Missing smokeless tobacco cessation outcome data will be imputed as "did not quit" for the Aim 1 and 3 primary outcome analyses applying the ITT principle. Aim 2 will apply hierarchical mixed-effects trajectory models to assess change in withdrawal symptoms, craving, self-regulation and restraint. Trajectory methods will allow missing outcome data when estimating participant trajectories. To test the data missing at random (MAR) assumption of trajectory methods, intervention group differences in missing rate at each time point and number of missing values across time will be compared using tests for difference in proportion or cumulative counts. For missing covariate data in the models, imputation methods (e.g., multiple imputation) will be carefully applied as needed. The latter will be particularly important for the ITT analyses.

Sample Characteristics. Baseline sociodemographic and clinical characteristics (including tobacco use) will be described for the total sample and by intervention group (SGR vs control). Intervention group differences in baseline characteristics will be examined using t-tests for continuous measures and chi-square /Fisher's Exact tests for categorical variables. Although the randomization should balance the two intervention groups in terms of sample characteristics, the baseline analysis will be used to identify potential covariates to be included in the efficacy and mediation analyses. For example, significant baseline intervention group differences in percentage of participants from rural and/or medically underserved counties will be examined. Statistically non-significant baseline covariates will be omitted from the final analytic models.

Process Measures. Intervention adherence (response to SGR texts for intervention group) and (how often participants read the cessation booklet for control group) and intervention interaction (number of times participants texted the system) for the intervention group and the control group and the effect of these process measures on cessation outcomes will also be explored using correlational analysis. Intervention acceptability will also be examined and compared between arms.

Consideration of Biological Variables. Biological sex and age will be evaluated for their potential covariate or moderating effects on the outcomes regardless of whether the intervention groups

differ on these baseline characteristics (however we do expect a small number of women in the current study given the higher rates of

smokeless use in men)**.** Specifically, the main effect and interaction of each biological variable with intervention group will be tested. For each biological variable, statistically non-significant main and/or interaction effects will be omitted from the final analytic models. If there is a significant interaction (indicative of a moderating effect of the characteristic), the interaction and its component terms will be retained in the final model and a moderator analysis will be conducted applying the approach recommended by Kraemer et al.51 for clinical trials. For example, if there is a significant sex-by-group interaction effect, the moderating effects of sex will be further evaluated by testing for intervention effects within subgroups of the characteristic. We realize that our numbers of projected females for this study are small given nationally females use smokeless tobacco a very low rate (0.5%)11 and our pilot mirrored these results. Nonetheless, we will conduct analyses to address the influence of these biological factors on study outcomes if there is adequate heterogeneity of the characteristic to do so.

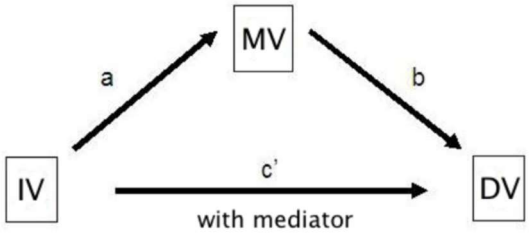
Aim 1 Statistical Analysis. We will use logistic regression without covariates to test for an intervention group difference (SGR vs control) in self-reported cessation at 6 months. Next, a covariate-adjusted analysis will also be conducted to evaluate identified potential baseline covariates and examine the impact of biological variables (e.g., age and sex and their interaction with group) on self-reported cessation at 6 months. Odds ratios (ORs) and their 95% Cis will be used to estimate effect size and address clinical significance. As a supplemental analysis, Generalized Estimating Equation (GEE) models for longitudinal binary outcomes will be used to test for intervention group differences in cessation trajectories across the 6 months, with *a posteriori* contrasts at each assessment point. Finally, we will compare self-reported and biochemically confirmed cessation outcomes obtained from 20% random sample of those who self-reported cessation at end of treatment and month 3 and 6. A z-test will be used to test for a group difference in the percent agreement at each time point.

Aim 2 Statistical Analysis. We will use hierarchical mixed-effects models for repeated measures with *a posteriori* contrasts at each time point to test for intervention group differences in the trajectory of changes in severity of craving, withdrawal, self-regulation, and restraints across time (baseline, end of treatment, 3 and 6 months post-intervention). Specifically, random coefficients regression model (RRM) for longitudinal data will be used to compare the rate and pattern of change of these outcomes across time. Fixed effects will be intervention group, time, and group-by-time, while random effects will be participant and participant-by-time. A covariate-adjusted analysis will also be conducted to evaluate the influence of baseline covariates and biological variables (e.g., age and sex effects and their interactions with group). The model will be fitted for significant non-linear change within one or both intervention groups. Intraclass coefficients across time along with Cohen *d* equivalents and their 95% CIs at each time point will used to address intervention effect sizes.

Exploratory Aim 3 Statistical Analysis. We will conduct mediator analyses using criteria recommended by Baron and Kenny52 as well as analytic guidelines from Kraemer et al.51 to explore whether changes in withdrawal symptoms, craving, self-regulation, and restraint mediate intervention group effects on tobacco use cessation across the 6-months. Each proposed mediator

will be evaluated separately (See **Figure 5**). First, the initial step of the formal mediation analysis will be to determine whether the intervention group significantly influences the trajectory of change in withdrawal symptoms, craving, self-regulation, and restraint (Path A). The Path A analysis will be completed in Aim 2. Second, logistic regression will be used to examine whether the slope coefficients for the individual trajectories of the proposed mediator are associated with cessation at 6 months (Path B). The final logistic regression model conducted for Aim 1 will be used to test for intervention group differences in cessation at 6 months post-intervention (Path C). Finally, the slope coefficients for the proposed mediator will be added as a covariate to the Path C logistic regression model (Path C'). The Path C' analysis will allow us to examine the effects of the intervention groups on Month 6 cessation after adjusting for the effects of change in the proposed mediator across time. For each proposed mediator of SGR effects, mediation will be established if the SGR group compared to the control group has significantly greater improvements in the mediator as an outcome (Path A), the degree of improvements in the mediator across time is related to cessation at 6 months (Path B), the SGR group has a significantly higher cessation rate at 6 months compared to the control group (Path C), and SGR effects on cessation are partially or fully diminished after adjusting for the mediator effect (Path C'). A Sobel's Test will be used to further determine the degree to which improvement in withdrawal, craving, self-regulation, and restraints mediate intervention effects. ORs and their 95% CIs will provide estimates of effect sizes.

Figure 5: Mediation Analysis Pathways



Statistical Power. The sample size of 500 (N=250 per intervention arm) will provide at least 90% power to address the primary aim (Aim 1), primary outcome (self-reported cessation at 6 months), and primary analysis (ITT analysis). A previous smokeless tobacco SGR study in smokeless tobacco resulted in a 27% cessation rate at 6-months.25 Our pilot resulted in a 22% cessation rate at 6-months. Given the improvements to our

SGR intervention, we conservatively estimate a slightly higher quit rate at 25% at 6-months. The Enough Snuff Control intervention has yielded quit rates between 16-18% at 6-months;43,44 however, these studies were clinic-based and deployed out of dental offices with military personnel, representing a different population and mode of delivery than we are proposing. A similar, web-based version of the intervention delivered remotely yielded quit rates of 12%.30 Given the low-touch remote nature of our study and the focus on rural and underserved populations, we expect quit rates in the control group to be closer to 12% at 6-months. Therefore, we estimate a medium effect at 6-months. In summary, the target sample size is based on the assumptions that: (1) logistic regression will be performed with two-tailed significance set at 0.05; and (2) the quit rate at month-6 may be as low as 25% in the SGR group and 12% in the control group at 6-months for the ITT analysis (odds ratio of 2.44, Cohen's *d* equivalent of 0.493, approximate medium effect); Consistent with prior smokeless intervention studies, the target sample size will not be adjusted for attrition rate and dropouts will be coded as continued to use. Based on these assumptions, a sample size of 250 per arm will provide 96% power to test the primary aim. If an attrition rate of 30%

is observed in each arm of the proposed study, the resulting sample size of 175 per arm will provide at least 80% power for the completers analysis for Aim 1.

Addressing scientific rigor and reproducibility. All final study procedures will be documented in detail with accompanying scripts, documents, examples and measures. Our assessments and reports will include descriptive statistics. The study PI will oversee the training of study staff and make sure all procedures meet high standards of fidelity using a checklist of key tasks with periodic observations of performance of tasks. Facebook recruitment quality control will be maintained by Dr. Noonan with consultation from Dr. Herbert Severson. Texting quality control standards will be maintained under the supervision of Dr. Noonan. Dr. Fish will oversee quality control of all assessment measures during the study. Further, the study statistician, Dr. Silva, will document data quality control standards and procedures (e.g., data checking).

Potential Risks and Challenges

Assessing adherence. A limitation of the SGR method is that we are not able to objectively determine if smokeless tobacco users actually chew/dip when they text that they do. We considered asking participants to video tape their smokeless tobacco use, but this is burdensome and may reduce intervention engagement. However, assessing adherence is important, and we will conduct daily check-ins at the end of the day via text to ask participants how many times they chewed/dipped that day and if they chewed/dipped off schedule. We will compare these data point to the texts we received throughout the day to verify adherence. In our pilot study, the majority (65%) of participants reported never or only a few times chewing/dipping off schedule. This limitation is outweighed by the multiple strengths of this study, including the focus on a population that has an obvious disparity and minimal access to effective smokeless tobacco cessation interventions.

Plans for non-adherence. Although we found in our pilot work that participants respond to most texts to chew/dip, we will encourage adherence. When participants do not respond to three texts in a row, we will send out a separate text reminding them to respond. Also, at the end of the week, we will send participants a text message letting them know the percentage of texts to which they responded (e.g., "You texted back 89% of the time when we texted. Good job! Try to get to 100%. Thanks so much!"). Those that respond to 80% of weekly texts will be entered into a weekly lottery for a $25 gift card. Given both groups have two-way texting and are requested to respond to texts, both groups will be entered into this lottery (during the active SGR period for the intervention group and during the 5 weeks of texting for the control group).

Cell phone issues. With any text-based intervention, loss of phone, phone disconnection, and reception are potential risks. We will assess for cell phone reception and possible service disconnection at baseline. We will continually monitor for cell phone problems by monitoring data received by participants to flag participants who have not reported data for extended periods, as well as by instructing participants to report issues to us.

Summary and Future Dissemination Plans

Our text-based SGR intervention has the potential to reach many at risk smokeless tobacco users. Robust preliminary data support the feasibility of our approach in achieving the study aims, and our

research team has a strong record of collaboration. The proposed five-year study **(see Study Timeline)** was designed to examine the effects of text-based SGR cessation compared to evidenced-based standard of care intervention among rural and medically underserved smokeless tobacco users. If this intervention is efficacious, it will be feasible to conduct an implementation trial. The intervention phase is completely automated and our program has the ability to enroll participants via the automated system for future dissemination trials. The long-term goal of this research is to decrease cancer-related morbidity and mortality by developing evidence-based tobacco cessation treatments that are easily disseminable for rural and medically underserved smokeless tobacco users.