Official Title: Optimizing hookah tobacco public education messages to reduce young adult use

NCT Number: NCT004242014

Study Protocol

Initial Approval: March 4, 2019

GEORGETOWN UNIVERSITY

APPROVAL

March 5, 2019

Darren Mays
dmm239@georgetown.edu

Dear Darren Mays:

On 3/4/2019, the IRB reviewed the following submission:

Type of Review:	STUDY
Title:	Randomized Trial Testing the Efficacy of Hookah Tobacco Public Education Messages among Young Adults
Investigator:	Darren Mays
IRB ID:	STUDY00000277
Review Type:	Non-Committee
Review Level:	Expedited
Review Category:	(7)(a) Behavioral research (7)(b) Social science methods
Funding:	Name: National Cancer Institute (NCI), Funding Source ID: R01 CA229082 01
Grant Title:	
Grant ID:	
IND, IDE, or HDE:	None
Documents Reviewed:	• FDA R01 Online ICF 021219.pdf, Category: Consent Form; • AmeriSpeak Email Invitation.pdf, Category: Recruitment Materials; • Hookah Education Messages.docx, Category: Any Other Study Related Documents; • Sun Education Messages.pptx, Category: Any Other Study Related Documents;

The IRB has approved the submission. You can begin research activities. **The approval is valid from 3/4/2019**. Any modifications to the IRB-approved protocol and other supporting documents must be reviewed and approved by the IRB prior to implementation.

If the study will continue beyond , please submit a continuation request form at least thirty (30) days prior to to allow the IRB sufficient time to review and approve the request.

In conducting this protocol, you are required to follow the requirements listed in the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within the IRB system.

Sincerely,

Michael Orquiza

PROTOCOL TITLE: Randomized Trial Testing the Efficacy of Hookah Tobacco Public Education Messages among Young Adults

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE: Version 1; January 31, 2019
Version 2; December 2, 2019

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	12/02/2019	Modify informed consent process	Yes

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GHUCCTS Questions

GHUCCTS is the Georgetown-Howard Universities Center for Clinical and Translational Science.

Is this study a GHUCCTS Study? ____Yes __X__No

Is the project being sponsored or funded by GHUCCTS? ____Yes __X__No

Does the project utilize GHUCCTS services or facilities? ____Yes __X__No
(e.g., is the study conducted on the Clinical Research Unit (CRU), is the study supported by a GHUCCTS biostatistician, etc.)

1.0 Study Summary

Study Title	Randomized Trial Testing the Efficacy of Hookah Tobacco Public Education Messages among Young Adults
Study Design	Two-group randomized trial study design to test message effects prospectively on young adults who are susceptible non-users of hookah tobacco and current users.
Primary Objective	To examine the efficacy of public education messages that target young adults' beliefs about hookah tobacco use in 4 domains: health harms, addiction, social use, and flavoring for preventing and reducing hookah tobacco use.
Secondary Objective(s)	NA
Research Intervention(s)/ Investigational Agent(s)	Education messages about the health harms, addictiveness, social use, and flavoring of hookah tobacco use.
IND/IDE #	NA
Study Population	Young adults between the ages 18 to 30, including young adults who are susceptible non-users of hookah tobacco and current users.
Sample Size	n = 1100 participants
Study Duration for individual participants	Approximately seven (7) months.
Study Specific Abbreviations/ Definitions	NA

2.0 Objectives*

2.1 The purpose of this study is to examine the efficacy of hookah tobacco public health education messages among young adults between the ages 18 to 30, including young adults who are susceptible non-users of hookah tobacco and current users.

2.2 Hypothesis 1: Messages will decrease hookah initiation among susceptible non-users and increase cessation among hookah users.

Hypothesis 2a: Message effects will be mediated by greater message engagement, message receptivity, and perceived harms of hookah tobacco.

Hypothesis 2b: Message effects will be greater among susceptible non-users versus hookah users and among those who do not use other tobacco products versus those who do.

3.0 Background*

3.1 The prevalence of regular (i.e., daily) and intermittent (i.e., some days, rarely) hookah tobacco use among US young adults rivals that of cigarette smoking and surpasses products such as electronic cigarettes.[1,2] Our previous work indicates nearly 30% of US young adults who do not use hookah are also at risk of initiation.[3] A typical hookah smoking session can last 1 hour or more and exposes users to harmful chemicals including at least 8 classes of carcinogens linked to lung, bladder, larynx, oral cavity, and esophageal cancer.[4-6] Long-term use increases the risks of cancer, lung disease, and other health outcomes, and hookah smoke exposure precipitates carcinogenesis in-vitro.[7,8] Hookah use among young people can also promote addiction: users report dependence symptoms, withdrawal, and difficulty quitting.[9, 10] Young adulthood is generally a vulnerable period for tobacco initiation,[11] a time when addictions unfold and transitions to regular tobacco use occur,[11] and there is growing evidence this occurs with hookah tobacco.[12-14] Young adults' hookah use is a critically important problem for tobacco control.[15]

The 2009 Family Smoking Prevention and Tobacco Control Act authorized the Food and Drug Administration (FDA) to regulate the marketing, sale, and manufacture of cigarettes, smokeless, and roll-your-own tobacco.[16] In 2016, FDA finalized the "deeming" rule bringing all tobacco products under its regulatory jurisdiction, including hookah tobacco.[17, 18] This rule subjects newly deemed products to regulatory measures of the Tobacco Control Act and also positions FDA to engage in public education to ensure consumers are informed of the risks of regulated products as required by the Tobacco Control Act.[16] FDA has launched mass media campaigns targeting youth cigarette smoking and evidence indicates they are positively affecting smoking behavior in target populations.[19] With the deeming rule finalized, FDA has announced plans to expand public education efforts to newly regulated products such as e-cigarettes,[20] and is positioned to do so for hookah as well. Importantly,

any FDA tobacco regulatory measures must be guided by the public health standard of the Tobacco Control Act: FDA must consider evidence of their impact on users and non-users, and especially young people. This study fills an important gap in the research guiding FDA public education efforts surrounding the risks associated with hookah tobacco use by testing the efficacy of messages among young adults, the primary population where hookah use occurs.

3.2 **Hookah Tobacco Message Development.** We have carefully developed and studied the effects of public education messages delivered online conveying harms and addictiveness of hookah tobacco use among young adult non-users who are susceptible to initiation and current hookah users. Our first step was to update message content from previous research[21] based on the recent literature. Then, we pretested revised messages with 46 young adults (Mean age 24.1, 41% female, 24% non-white) using online crowdsourcing. Participants rated revised message content highly (1 to 7 scale) on relevance (Mean 5.5), believability (Mean 5.2), applicability (Mean 5.4), accuracy (Mean 5.6), understandability (Mean 5.6), and importance (Mean 5.2). In a separate sample of 44 young adult hookah users (Mean age 25.3, 53% female, 20% non-white), we also assessed message content preferences, finding messages conveying risks of harm and addiction resonate with this group.[22] The proposed approach builds directly for our prior work to carefully develop education messages targeting young adults' hookah use.

Message Effects: Susceptible Non-Users. We experimentally examined effects of the revised messages in 508 young adults who never used hookah tobacco (M age 25.3, 50.1% female, 199% non-white) recruited online, 248 (49%) of whom were susceptible to initiation.[23] Participants exposed to the messages responded favorably on measures of engagement, and those who were susceptible to using hookah tobacco indicated message content was more personally relevant than those who were not susceptible ($p < .001$). Overall, compared to young adults receiving no message content, those viewing study messages reported greater perceived harm and addictiveness ($d = .89$) of hookah tobacco, greater worry about harm and addiction ($d = .30$), and more negative attitudes toward hookah ($d = .30$). Among susceptible young adults, those viewing messages reported less intention to try hookah tobacco in the future compared to those not exposed to messages ($d = .34$, $p = .035$); there was no significant effect of messages on hookah use intentions in non-susceptible young adults. These data support our objective to test message efficacy among young adults who are susceptible non-users of hookah tobacco.

Message Effects: Hookah Users. We also tested message effects in 327 young adult hookah tobacco users (Mean age 24.8, 38% female, 22% non-white) recruited online.[24] Participants completed pre-exposure measures and were randomized to a control condition receiving no messages (n = 108), a condition receiving messages about hookah tobacco harms (n =

107), or a condition receiving messages about hookah tobacco harms and addictiveness (n = 112). Post-exposure measures captured hookah tobacco perceptions and motivation to quit. Main effects for study condition were statistically significant for all outcomes ($p \leq .001$) except perceived risk of addiction ($p = .051$). Pair-wise mean comparisons showed participants in conditions receiving study messages endorsed stronger perceived harm (d's .74-.79) and addictiveness (d's .47-.80), greater worry about harm (d's .42-.44) and addiction (d's .31-.47), and stronger motivation to quit (d's .22-.47). Message effects on motivation to quit were mediated by greater worry about harm and addiction.[35] These findings demonstrate the potential for public education messages to affect relevant cognitive and behavioral outcomes in young adult hookah tobacco users.

3.3 There is extremely limited research on optimal message content for hookah tobacco, particularly research addressing the evidentiary standard set forth in the law. The FDA and NCI have for this reason identified young adults as a priority population for studies of non-cigarette product use such as hookah and communication interventions.[25, 26] Our study addresses a critical research need in FDA's priority area of Communications by rigorously and comprehensively identifying optimal content for hookah tobacco public education messages and determining effects on behavioral outcomes in susceptible young adult non-users and current hookah users.

Evidence-based public education messaging is a recommended component of comprehensive tobacco control efforts.[27] For cigarette smoking, strategies such as mass media campaigns and warning labels on product packaging are effective for preventing smoking uptake and promoting cessation.[28-30] Young adults' hookah use is characterized by unique perceptions and beliefs about the harms and addictiveness of hookah tobacco, beliefs that social use poses little risk, and is fueled by the wide array of appealing flavors that are commonly used by young people.[31-42] Messages aimed at these factors are needed to dissuade initiation among non-users and motivate users to quit.[43] However, hookah tobacco use predominantly occurs in cafés and other social settings, limiting users' exposure to regulatory communications such as warning labels on product packaging.[18, 31] Our research indicates public education messages conveying health harms and addictive potential of hookah use resonate with young adults, decrease intentions to use hookah among susceptible non-users, and increase motivation to quit among current users.[23, 24] Our preliminary findings described above on hookah message effects are promising, but research examining strategies to optimize message impact is sorely needed.

4.0 Study Endpoints*

4.1 The primary study endpoints among susceptible non-users are changes in susceptibility to use hookah tobacco, curiosity (i.e., intentions) to use hookah tobacco, and hookah tobacco initiation. The primary end

points among current hookah users are motivation to quit using hookah tobacco, frequency of hookah use, and cessation.

4.2 Secondary end points include perceived harm & addictiveness of hookah tobacco, perceived risk and worry about harm & addictiveness, and message-related outcomes including message receptivity, emotional response, and content recall. These will be examined as mediators of message effects. There are no safety outcomes in this trial.

5.0 Study Intervention/Investigational Agent

1.1 The study intervention is public health education messages that convey the health harms, addiction, social use, and/flavorings associated with hookah tobacco use.

6.0 Procedures Involved*

6.1 This study is a two arm prospective randomized trial to test the efficacy of public health messages about hookah tobacco use. All study procedures will be conducted by NORC staff in direct collaboration with the study team and investigators. Study participants will be anonymous to the study team and investigators, and all data collected as part of the study will de-identified.

Participants will be recruited from the National Opinion Research Council's (NORC) AmeriSpeak consumer market research panel, screened for eligibility, and will complete a baseline assessment online. Then participants will be randomized in equal numbers to two arms: 1) hookah tobacco public education messaging or 2) control arm. On approximately a weekly basis for 4 weeks, participants will receive study communications and complete brief measures of message response online. For the hookah tobacco public education messaging arm, communications will consist of the study messages communicating about the health harms, addictiveness, social use, and flavorings in hookah tobacco. In response to each message, participants will complete measures of message response and hookah-related outcomes detailed below. Participants in the control condition will receive study communications with brief messages about health behaviors unrelated to tobacco (sun protection) and will complete the same measures. Study outcomes and hypothesized mediators will be assessed 2-, 4-, and 6-months after the message exposure period.

6.2 Trial participants will be 1,100 English speaking young adults ages 18 to 30 years old who have never used hookah tobacco but are deemed susceptible based on four screening questions or report hookah tobacco use at least once within the past month on valid measures. Trial participants will be recruited from the AmeriSpeak national consumer research panel maintained and operated by NORC. Although recruitment and data collection procedures will be conducted by NORC and all study participants will be anonymous to the investigators, our team will work collaboratively with NORC AmeriSpeak staff to oversee recruitment,

enrollment, data collection, and experimental procedures.

AmeriSpeak panel members who are young adults ages 18 to 30 in the US will be sent a standard email invitation describing the study. Potential participants are identified by randomly selecting households within the panel with a young adult within the study age range, and targeting study invitations based on recent study participation, and other demographic characteristics as needed to ensure a representative sample. This email invitation will introduce study procedures and eligibility criteria, and direct interested panel members to the eligibility screener with items to confirm eligibility. Procedures will ensure potential participants are adults ages 18 and older through two steps: 1) targeting study invitations only to those panel members whose age is within this range; and 2) re-assessing age at eligibility screening and excluding those who provide inconsistent information (i.e., ages differ in self-reported screening compared with panel-based age derived from date of birth). Panel members who are confirmed to meet study eligibility criteria will proceed to the online baseline. AmeriSpeak panel members who do not meet study eligibility criteria will be redirected to a concluding thank-you screen. Similar procedures will be followed when participants are contacted for the brief message exposures and the 2-, 4-, and 6-month follow-up assessments. This approach is guided by similar previous tobacco research studies with young adults, including studies with prospective participation and retention rates of 70% and higher.[45-46]

The online baseline assessment includes valid measures of hookah and other tobacco use behavior, hookah beliefs, perceptions, and other constructs from our conceptual framework. After completing a baseline, participants will be randomly assigned in approximately equal numbers to one of two arms: 1) hookah tobacco education messaging; 2) control arm. Randomization will be balanced by hookah use status (susceptible non-user, current user) to ensure sufficient numbers of these characteristics across study arms. Participants in the hookah education messaging arm will then receive 4 study communications delivered approximately weekly during the exposure period. These communications will consist of: 1) the study hookah education messages; and 2) brief post-message (approximately 5 minutes) measures of hookah use behaviors, beliefs and perceptions, and message responses. Procedures for participants randomized to the control arm will be similar, however communications will consist of non-tobacco messages communicating about sun protection that we have developed on our previous work and pilot tested against tobacco-related messaging to ensure they are an adequate contact-matched control. Messages will have a similar layout and structure (e.g., amount of text) to the hookah public education messages and will be presented in a consistent order for all participants. We chose this contact-matched control arm to ensure groups are treated equivalently with only message content varying between arms.

All participants will complete follow-up assessments online 2-, 4-, and 6-months after the message exposure period. We chose these time points based on our team's prior work on young adult tobacco use behavior and messaging,[44, 45] other research on hookah tobacco messaging,[21] recommendations for follow-up in tobacco intervention research,[47, 48] and because this follow-up frequency and duration will capture short term message effects and changes in hookah use, susceptibility, and mediating processes.[12, 14, 21, 47, 49-52] As with the baseline, follow-ups will be securely administered online. Measures are attached in Section 14. At the conclusion of the final follow-up, all participants will be debriefed on the study goals and the potential risk of hookah and other forms of tobacco use.

6.3 Although the study presents minimal risks to participants, we have carefully developed a plan for mitigating and addressing potential risks. We will not collect or have access to any participant identifying information as part of the study; all participants will be anonymous to the investigators protecting their privacy and confidentiality. Due to the nature of study, the primary potential source of risk is the gathering of social and behavioral information about tobacco use. We recognize that protecting participants' privacy and confidentiality is most salient and have study procedures in place to protect this information. Although we will not collect identifying information and all participants will be anonymous to the research team, we have several safeguards in place to protect participants' privacy and ensure that all study data are treated as secure and confidential.

First, all NORC AmeriSpeak panel members provide their consent to participate in research studies that NORC conducts on behalf of clients upon joining the panel and are provided with details of NORC's privacy and data protection policies and procedures. The consent form provides contact information for NORC staff if participants have questions about the study or encounter any issues surrounding study participation. Participants may call or email NORC staff with any questions, concerns, or problems related to the study. This consent document and NORC's policies and procedures are attached to the protocol.

Second, at the beginning of all study assessments, we will emphasize the voluntary and confidential nature of participation and that no personally identifying information will be collected by or released to the investigators conducting this research.

Third, in the unlikely event that a participant in the study contacts NORC staff with questions or to report issues, we will work with NORC staff to determine a resolution. Although they are unlikely and we have not experienced such an occurrence in our research to date, any unexpected adverse events will be recorded and reported to the Georgetown IRB as detailed below describing aspects of our Data Safety and Monitoring Plan.

6.4 All study data will be obtained by participants' self-report responses

to anonymous online surveys. Data will be collected on hookah and other tobacco use behavior, hookah beliefs, perceptions, and responses to study messages.

7.0 Data and Specimen Banking*

NA – No specimens are collected as part of this study.

8.0 Sharing of Results with Subjects*

8.1 We will not have the ability to contact participants given the anonymous nature of the study.

9.0 Study Timelines

9.1 The duration of an individual's participation in the study to complete all procedures is approximately 7 (seven) months. We anticipate it will take approximately 12 months to enroll participants and complete data collection. We anticipate primary analyses will be completed by April 30, 2022.

10.0 Inclusion and Exclusion Criteria*

10.1 NORC AmeriSpeak panel members will be recruited and screened for eligibility through a series of steps. NORC will send an email invitation using their standard template to potential participants and will introduce study procedures and eligibility criteria to AmeriSpeak panel members. Interested panel members will be directed to the online eligibility screener with valid self-report items to confirm eligibility. Invitations will be targeted by NORC using data from the member panel enrollment profile (i.e., participant age) and confirmed based on responses to the brief online eligibility screener.

10.2 Eligible participants for the randomized trial will be 1) young adults ages 18 to 30; 2) who have never used hookah tobacco but are deemed susceptible based on 4 screening questions or report hookah tobacco use at least once within the past month based on valid measures;[23, 24] and 3) are NORC AmeriSpeak panel members residing in the US.

Study exclusion criteria include: 1) individuals who are younger than 18 or over 30 years of age; 2) those who do not meet self-report criteria for susceptibility or current use of hookah tobacco; or 3) are not registered to participate in research studies through the NORC AmeriSpeak panel.

10.3 Study participants will be Amerispeak panel members who meet the eligibility criteria listed above. The following special populations will be excluded: Adults who are unable to consent, individuals who are not yet adults, pregnant women, and prisoners.

11.0 Vulnerable Populations*

N/A

12.0 Local Number of Subjects

12.1 Our sample size is 1100 participants, including 425 young adult hookah users and 675 susceptible non-users. We conducted power analyses as described in Section 17 to determine the target sample size.

13.0 Recruitment Methods

13.1 The sample will be recruited through AmeriSpeak national consumer market research panel maintained by NORC. Recruitment and data collection procedures will be conducted by NORC under Dr. Mays's supervision; however all study participants will be anonymous to the investigators and NORC research staff will conduct all procedures using standard protocols. Participants will be recruited from the AmeriSpeak national panel through email invitations. This email invitation will introduce study procedures and eligibility criteria and interested panel members will be directed to the eligibility screener as described above.

13.2 The source of participants will be NORC's AmeriSpeak panel. Participants must be AmeriSpeak panel members. All study recruitment and data collection will be conducted by NORC; participants will be anonymous to the investigators and research staff.

13.3 Potential participants through NORC are identified by randomly selecting households within the panel with a young adult within the study age range, and targeting study invitations based on recent study participation, and other demographic characteristics as needed to ensure a representative sample.

13.4 A standard email invitation will be used to recruit participants. NORC's email template is attached to this application.

13.5 Participant incentives will be administered by NORC according to their standard procedures for panel members' survey participation. Panel members receive incentives in the form of "points" for completing study milestones, which can be accumulated and redeemed for gift cards, cash, and other rewards. For this study, incentives will be administered by NORC in the form of "points" at the completion of study milestones including baseline, weekly surveys, and the 2-, 4-, and 6-month follow-ups.

14.0 Withdrawal of Subjects*

14.1 AmeriSpeak panel members may choose to complete study procedures or not. Reasons for which participants may choose to discontinue participation in the study may include loss of interests or lack of time to complete remaining procedures. There are no foreseeable circumstances where the investigators or research team will withdrawal participants without their consent; we will not have the ability to directly communicate with participants since all participants are anonymous to the research team.

14.2 Participants who voluntarily withdrawal from the study will choose to on their own. There are no procedures for termination.

14.3 The only manner in which participants will withdrawal is if they decide to on their own. There will be no partial withdrawal with continued data collection in this study.

15.0 Risks to Subjects*

15.1 This study does not involve drugs, devices, or medical procedures. The primary potential source of risks in this study is the social risk of gathering behavioral information about tobacco use and tobacco-related attitudes, perceptions, and beliefs. These include potential embarrassment and fear of disclosure of potentially sensitive information, and confidentiality concerns.

16.0 Potential Benefits to Subjects*

16.1 There are no direct benefits to young adults who choose to participate in this research. The knowledge gained from the study will help us to understand how to best design hookah tobacco public education messages to prevent and reduce hookah use among young adults in the future.

17.0 Data Management* and Confidentiality

17.1 We calculated statistical power to test our study hypotheses assuming a two tailed $\alpha = .05$ and baseline sample of 1100 participants, including 425 young adult hookah users and 675 susceptible non-users. We estimated the ability to detect effects of the messages on hookah initiation among susceptible non-users[44] and cessation among current users[21] based on prior studies. Among susceptible non-users, we estimate 8% will initiate hookah use over the 6-month follow-up period based on our recent national study of US young adults.[44] With susceptible non-users at 6-month follow-up we will have 80% power to detect percent differences as small as 5.3%, or initiation of 8% in the control arm and 2.7% in the messaging arm. This equates to an odds ratio of 0.62 comparing hookah initiation between the messaging and control arms in a logistic regression analysis including covariates. Although evidence on hookah tobacco cessation rates is limited, 1 prior study found that young adult hookah users exposed to risk-based messages were nearly 2 times more likely than those in a control condition with no message exposure to report cessation at 6-month follow-up (62% vs. 33%, odds ratio 1.89).[21] Conservatively assuming a much lower overall cessation rate of approximately 10% (i.e., comparable to those of behavioral smoking cessation interventions)[53] the sample of hookah users at the 6-month follow-up will have 80% power to detect absolute differences in cessation between study arms as small as 8% (10% control, 18% messaging). In a logistic regression analytic framework with covariates, this equates to an odds ratio of 1.55. For analyses of continuous outcome variables, our sample will provide 80% power to detect small mean differences ($d \leq 0.10$) between arms in the complete sample, and among susceptible non-users and current users separately. For testing mediating effects,

simulation studies provide estimated power to detect mediation effects using bias-corrected bootstrap analyses.[54] The sample will provide 80% power to detect small- to medium- indirect (i.e., coefficients in the range of 0.20-0.30) effects. Similarly, for analyses of the interaction between study condition and two-level moderators we will have 80% power to detect moderator effects as small as Cohen's $f \leq 0.10$ in ANCOVA analyses (i.e., differences between susceptible non-users and hookah users) and odds ratios as small as 1.70 for interactions between non-hookah tobacco use and trial arm for binary initiation and cessation outcomes.

The primary outcomes and analytic approach will compare differences in 6-month outcomes across the control and messaging arms. We will initially assess differences in past 30-day hookah use behavior using longitudinal mixed effects logistic regression in the entire sample. The model will include past 30-day hookah use at 6 months as the dependent variable, trial arm, and baseline covariates for susceptible non-user/current user and any others identified in the steps outlined above.[55] We will then use a similar modeling strategy to assess differences by trial arm in hookah use initiation among participants who were susceptible non-users at baseline, and cessation among baseline users. These analyses will model dependent variables reflecting change in hookah use status from baseline to the 6-month follow-up separately for these two groups, a term for trial arm, and any covariates as identified above. Among susceptible non-users at baseline, we will similarly analyze changes in susceptibility status relative to trial arms as a secondary outcome. In both susceptible non-users and hookah users, will also conduct analyses to assess message effects on continuous outcome measures at 6 months, curiosity to use hookah tobacco and motivation to quit, respectively. We will use repeated measures ANCOVA to compare means of the continuous outcomes by trial arm at 6 months and Tukey's adjustment method for the pair-wise comparisons. In exploratory analyses, we will repeat these types of mixed logistic and ANCOVA analyses for outcomes measured at the 1- and 3-month time points. We will assess any potential message order effects separately in the education messaging arm by examining message effects by the 4x4 Balanced Latin Square orders. If any message order effects are detected or trends are observed we will include order as a covariate in analyses.[56] Exploratory analyses will also examine if responses to weekly assessments differ by message themes using approaches similar to those above.

We will test hypotheses about potential mediation of message effects through a series of steps drawing from traditional mediation frameworks for preliminary analyses[57] and applying more robust methods to formally test for mediation.[58] First, we will examine differences in means for mediating variables by trial arms and investigate whether each mediator at 1- and 3-month time points is correlated with the outcomes at 6-months using bivariate statistics and regression-based analysis accounting for any covariates as needed. Where these preliminary steps indicate potential mediation, we will formally test for mediation by estimating the indirect effects of candidate mediators at 1- and 3-months on study outcomes at 6-

months via the study arms using a bias-corrected bootstrapping method with 1,000 resamples to address non-normality of the product of the coefficients estimator.[54, 58] This bootstrapping approach estimates an indirect (i.e., mediation) effect reflecting the product of the effect of trial arm on the mediator with the effect of the mediator on the outcome, and produces bias-corrected asymmetric 95% confidence intervals (CIs) that correct for non-normality of the distribution of indirect effects.[58] This method provides higher power and better control over the Type I error rate compared with traditional approaches for testing mediation.[172,173] Asymmetric 95% CIs for indirect effects that do not include zero will indicate significant mediation effects.[172] We will evaluate hypothesized moderators individually by introducing them one at a time and their corresponding interactions with trial arm into the logistic regression and ANCOVA models. Analyses assessing differential effects of messages among susceptible non-users and hookah users will primarily be ANCOVA based and examine mediators and outcomes measured commonly in these groups. Although the primary moderators of interest are those relating to hookah and other tobacco product use, we will also explore potential moderating effects of participant demographics including sex (male, female) and age (< 25, 25+) and other characteristics in analyses.

17.2 NORC also takes extensive measures to ensure that all panel members' privacy and personal information are treated confidentially and kept secure. All personally identifying records are kept secured in a separate data servers maintained by NORC. NORC never provides any panel members' personally identifying information to a research partner without the explicit and informed consent provided by the sampled members. For this study, all data will be de-identified and anonymous to the investigators and no personal information will be released to the investigators, therefore there will be no way to discern participants' identities from the study data. All NORC survey response data are identified only by an anonymous ID number.

17.3 In addition to the measures put into place by NORC, our research team will take several additional steps to ensure data collected from AmeriSpeak panel members are treated as secure and confidential at GUMC. First, as noted above, all data will be anonymous and will not include personally identifying information. Any data to be transferred from NORC to Dr. Mays at GUMC/LCCC will use Georgetown Box. We will use Georgetown Box to transfer data files and documentation to Dr. Mays by creating a restricted access link that is password protected and only accessible to authorized NORC personnel. Second, once study data are transferred to GUMC/LCCC all electronic study data files will be securely stored on a GUMC/LCCC network drive. This network space is encrypted and directories are password-protected at the individual user level to ensure electronic data files are treated as secure and confidential. Only the GUMC/LCCC Principal Investigator and authorized study

personnel will be granted access to the data after appropriate permissions are established.

17.4 All study procedures use well-validated assessments with established psychometric properties. Quality control will be ensured by working with NORC to review online assessments we provide to ensure they function properly in terms of item performance, skip logic, and design. There are no other necessary quality control measures.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

Although all participants are anonymous to the study team and the procedures pose minimal risks, we have procedures in place to ensure data are treated as confidential and private and to protect participants.

Although they are unlikely and we have not experienced such an occurrence in our research to date, monitoring study progress and safety of participants is ongoing throughout data collection. Any unexpected adverse events will be recorded and reported to the Georgetown IRB. Despite that this study presents minimal risks for participants, the Principal Investigator, Dr. Mays, will actively work with NORC staff to monitor for any unanticipated adverse events. Dr. Mays will be responsible for evaluating any unanticipated problems that arise during the study and determining whether they affect the risk-benefit ratio of the study, and whether modifications to the protocol are required. Dr. Mays will be responsible for reporting any unexpected adverse events involving any aspect of the study to the Georgetown IRB per institutional guidelines. Unanticipated problems to be assessed include adverse events, deviations from the study design or protocol, and confidentiality violations. Dr. Mays will report unanticipated problems to the Georgetown IRB within 3 business days of their occurrence.

NORC panel members who participate in this research may call a NORC-maintained and staffed telephone number with any questions or to report problems related to this study. This is a toll free number that is provided to all panel members in the privacy statement and during the informed consent process when they join the AmeriSpeak panel. Participants may similarly contact NORC via email (privacy@amerispeak.org).

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 The online consent form that AmeriSpeak panel members sign upon joining the panel emphasizes the voluntary and confidential nature of panel members' participation in research conducted by NORC and that NORC does not share personally identifying information with clients for whom they conduct research. At the beginning of all study assessments we reiterate the voluntary and confidential nature of participation, and that participants may withdraw at any

time without penalty. The research team does not have access to and will not collect identifiable personal information. Participants are permitted to skip any survey questions that make them feel uncomfortable and can withdraw from the study at any time.

19.2 In order to protect privacy of participants, access to study data will be strictly controlled by the PI and will only be accessible by study personnel with permission and training to do so. Participants will have an anonymous ID associated with their survey data to ensure their privacy. The anonymous ID does not include any personally identifiable information. Additionally, no private health information will be collected or recorded in this study. All online questionnaires completed and gathered as part of this study will be anonymous and no personally identifying information will be recorded on the questionnaires. Furthermore, only if participants have study-related questions about their rights as a research participant they may contact the Georgetown University IRB and with other study related questions they may contact NORC. The PI will work with these entities to resolve any questions or issues that may arise without direct contact with study participants to maintain anonymity.

20.0 Compensation for Research-Related Injury

NA

21.0 Economic Burden to Subjects

21.1 There are no costs to participants for their participation in this research.

22.0 Consent Process

22.1 NORC receives consent from panel members at the time the join the AmeriSpeak panel to participate in research they conduct on behalf of clients. For this study, procedures involve completing an online survey about tobacco use behaviors and cognitive responses to tobacco-related messages. All data will be de-identified and participants will be anonymous to the investigators. There will be no way to link individual participants to their answers to survey questions. These procedures present minimal risks to participants. Given the anonymous nature of study participation, and participant recruitment and data collection through NORC, we will use NORC's online informed consent process that they have in place for panel members. Additionally, we have put into place rigorous procedures to treat data collected for this study as private and confidential in accordance with data management procedures.

22.2 Waiver of Consent Justification: The research presents no more than minimal risk of harm to participants. All study procedures will be conducted by NORC and participants will be anonymous to the investigators and study team. Therefore it would not be practicably feasible to obtain written informed consent from participants.

23.0 Process to Document Consent in Writing

23.1 The research presents no more than minimal risk of harm to participants and involves no procedures for which written documentation of consent is normally required outside of the research context.

24.0 Setting

24.1 Study procedures will occur online and will be directly managed by staff at NORC in collaboration with the research team at the Lombardi Comprehensive Cancer Center (LCCC). No personally identifying information will be collected for any part of this research, and all study participants will be anonymous to the investigators.

25.0 Resources Available

25. 1 Participants will be recruited from the NORC AmeriSpeak national consumer market research panel maintained by NORC. NORC is an independent research institution that specializes in data collection for academic and government research. AmeriSpeak is a probability-based consumer research panel designed to be representative of the U.S. household population. Panel members participate in studies conducted by NORC or those conducted by NORC on behalf of government agencies, academic researchers, and other organizations. Through partnerships with academic and government researchers, NORC has been actively involved in public health and health sciences research. Study procedures will be conducted by NORC under Dr. Mays's supervision. Dr. Mays will work collaboratively with NORC AmeriSpeak staff to oversee recruitment, enrollment, data collection, and experimental procedures. Dr. Mays has engaged with NORC in preparation for the NIH grant application supporting this study to ensure feasibility of the proposed research. Our research team is highly experienced in conducting online, behavioral studies on tobacco use and related messages to ensure the study is feasible and successful.

26.0 Multi-Site Research*

NA