Study protocol with statistical analysis plan

Official Title of the study: Understanding health warning effects on waterpipe (hookah) smokers' experiences and exposures

NCT number: Not applicable

Date of the document: November 13, 202**0**

Title: Developing and testing waterpipe-specific health warning labels targeting young people in Florida.

General Audience Abstract: (3,492/3,500 characters)

Waterpipe (WP) smoking (a.k.a. hookah) has become one of the leading tobacco use methods among youth in Florida. The impact of this dramatic rise is likely amplified by the mounting evidence of WP addictive and harmful nature, as well as the lag of policy response to it. Evidence suggests WP use leads to nicotine addiction, and increases the risk of lung cancer, heart and respiratory disease and exposure to secondhand smoke. The spread of WP use among youth has been fueled by a misperception of reduced-harm compared to cigarettes. Health Warning Labels (HWLs) represent one of the most successful tobacco control strategies to communicate smoking-related risks, and studies have consistently shown that HWLs are associated with a decrease in smoking rates and smoking-related morbidity and mortality. Therefore, communicating WP risks to young people through HWLs has been identified as a priority by major health bodies in the US including the FDA.

Currently, the FDA requires that WP tobacco packages have a textual HWL: *"WARNING: This product contains nicotine. Nicotine is an addictive chemical."* While this represents a good step, it is inadequate given the; 1- limited contact WP smokers have with tobacco packaging, 2- the established harm of WP smoking beyond tobacco (e.g., charcoal), and 3- the superior performance of pictorial HWLs over text-only ones. Therefore, pictorial WP-specific HWLs involving other WP components (e.g. device) are expected to be more effective in communicating risks to WP smokers. Using the Delphi method among tobacco control experts, our team has developed a set of 12 WP HWLs corresponding to 4 health themes (health risks and addiction, harm to others, WP-specific harm, WP harm compared to cigarettes).

Building on this work, and using a mixed-method approach incorporating qualitative and quantitative research, we propose to adapt the developed HWLs to young WP smokers in Florida and test them to answer an important policy question: Are pictorial HWLs on the WP device more effective than no-HWL (control) in increasing harm perception and intention to quit, and reducing smoking satisfaction, intensity, and exposure to toxicants? Accordingly, we will recruit young (18-29 yrs) WP users to:

1. Conduct 6-8 mixed-gender focus groups (n ≈ 65) to adapt the 12 HWLs to our local population of young adults on risk communication, explore optimal HWLs placement and size, and select the top 4 HWLs for testing in Aim 2.
2. Conduct a clinical lab experiment among 248 WP smokers categorized according their use frequency (beginner vs. established smokers) to test the performance of the top 4 HWLs on the WP device compared to no-HWL (control) on harm perception, intention to quit, puffing behavior, dependence (e.g. satisfaction, withdrawal), and toxicant exposure (CO, nicotine, oxidative stress). Three months later, participants will receive a phone call to assess longer-term adaptations as a result of exposure to HWLs (e.g. quit intention, quitting).
3. Partner with *Golin, Tobacco-Free Workgroup, and Truth Initiative* to advocate for the adoption of HWLs policies and disseminate knowledge about WP harmful effects to young people in Florida and nationally.

Communicating WP risks through HWLs promises to reduce WP use and WP-related morbidly and mortality among young adults in Florida. This pioneering work will provide the first evidence-based WP HWLs to advance WP control in Florida, and a model for other states to respond to the WP epidemic.

Scientific Abstract: (2,083/2,100 characters)

Waterpipe (WP) smoking has become one of the leading tobacco use methods among youth in Florida. The impact of this dramatic rise is amplified by the mounting evidence of WP addictive and harmful nature, as well as the lag of policy response to it. Evidence suggests WP use leads to nicotine addiction, and increases the risk of lung cancer, heart and respiratory disease and exposure to secondhand smoke. The spread of WP use among youth has been fueled by a misperception of reduced-harm compared to cigarettes. Health Warning Labels (HWLs) represent one of the most successful tobacco control strategies to communicate smoking-related risks, and studies have consistently shown that HWLs are associated with a decrease in smoking rates and smoking-related morbidity and mortality. Therefore, communicating WP risks to young people through HWLs has been identified as a priority by major health bodies in the US including the FDA.

Using the Delphi method among international tobacco control experts, our team has developed a set of 12 WP HWLs corresponding to 4 health themes; health risks/addiction, harm to others, WP-specific harm, WP harm compared to cigarettes. Building on this work, and using a mixed-method approach incorporating qualitative and quantitative research, we propose to:

Aim 1: Adapt the 12 HWLs to young WP smokers in Florida using exploratory focus groups.

Aim 2: Test in a clinical lab experiment the performance of the top 4 HWLs on the WP device compared to no-HWL/control on harm perception, intention to quit, and toxicant exposure (CO, nicotine, oxidative stress).

Aim 3: Use the knowledge obtained to advocate for the adoption of WP-HWLs policies and disseminate information about WP harmful effects to young people in Florida and nationally.

Communicating WP risks through HWLs promises to reduce WP use and WP-related morbidly and mortality among young adults in Florida. This pioneering work will inform the FDA and public health advocates on the potential of WP-HWLs policies and provide a model for other states to respond to the WP epidemic.

Health Impact: (3,464/3,500) characters

The rise of waterpipe smoking among young people in the US has been fueled by a widespread misperception of "reduced-harm" compared to cigarettes (Bhatnagar 2019). Evidence suggests WP smoking carries similar health risks as cigarettes. Moreover, unique risks of WP can stem from the contribution of charcoal (e.g. carcinogens), device and accessories (e.g. infectious disease) (CDC 2018). Compared to one cigarette, a single WP session involves exposure to 150-180 times the amount of smoke (≈90,000 ml of smoke for WP vs. 500-600 ml for cigarettes), 1.7 times the nicotine, 8.4 times the CO, and 36 times the tar (Cobb 2010). Evidence from systematic reviews shows that WP smoking is associated with increased risk of lung cancer, and major cardio-pulmonary diseases (Jawad 2013, El-Zaatari 2015, Waziry 2016).

Given that health warning labels (HWLs) represent a cornerstone strategy to communicate smoking-related risks and reduce cigarette-related morbidity and mortality (Noar 2016, a), leading public health and tobacco control bodies in the US consistently advocated for WP-specific HWLs as a priority to reduce WP smoking and related health risks (CTP-FDA 2012, WHO 2015, FDA 2017). However, there have been no systematic efforts to develop WP-specific HWLs. Our team has started to address this gap, and this project builds on that work to develop pictorial WP-HWLs with the involvement of young WP smokers in Florida. We will then test these HWLs on important policy/regulatory outcomes (e.g., harm perception, intention to quit, exposure to toxicants).

Communicating WP associated risks through HWLs promises to reduce WP smoking and WP-related morbidly and mortality in Florida and nationally. Experience with using HWLs for cigarettes in Canada for example has resulted in 12-20% reduction in smoking prevalence and nearly 5,000 fewer smoking-attributable deaths annually (Azagba 2012, Huang 2014). Similarly, implementing HWLs policy in Ireland and the Netherlands in 2008 resulted in 464,493 fewer smoking-attributable deaths by 2010 (Nagelhout 2012, Currie 2013).

HWLs can be expected to reduce tobacco-related health disparity as well, since their effect on reducing smoking-associated deaths was stronger among lower socio-economic groups in several countries, including the US (Van Minh , Mead 2015). Moreover, concerns about the "wear out" of HWLs effect is not substantiated by evidence, which shows that such effect is sustained years after the policy implementation (Huang 2014, Van Minh 2016). Even among those who tried to avoid noticing the HWLs, smoking prevalence was reduced by 12% and intention to quit increased 1.5 times two years after the HWLs implementation (Van Minh).

This project will provide WP HWLs adapted for young WP smokers in Florida to advance WP-HWLs policies and disseminate knowledge about WP harmful effects to young people in Florida and nationally. We expect our work to inform the FDA, policymakers and public health advocates on the potential of WP HWLs to curtail WP smoking and protect young people from this emerging public health problem. We also expect this work to become the foundation for further research in this field to evaluate other domains related to WP-HWLs, such as WP venues-based warnings (e.g. on the menu), and web-based warnings for WP café's websites and WP internet retailers.

Tobacco Relatedness: (1971/2,100 characters)

Compared to nonsmokers, WP smokers have a 2-3 times increase in respiratory disease (e.g., COPD), 4 times increase in oral cancer risk, 2 times increase in lung cancer, and 3 times increase in cardiovascular disease (Jawad 2013, El-Zaatari 2015, Waziry 2016). Furthermore, the use of charcoal to heat the tobacco in the WP results in additional exposures to high levels of carbon monoxide, metals, and cancer-causing chemicals (Monzer 2008, Nguyen 2013, CDC 2018). Smoking in a group setting and sharing the same WP can furthermore, expose users to communicable diseases risks (e.g., tuberculosis, herpes) (Martin 2009, CDC 2018). WP smoking also releases secondhand smoke, which can be a health risk particularly to children living in WP smoking homes (Fromme 2009). Therefore, this project is highly responsive to tobacco-related cancer, cardiovascular and pulmonary disease.

WP-related health-damaging profile is consistent with the health effects of cigarette smoking, indicating that WP smoking is an important tobacco-related public health problem. By communicating these risks and providing evidence of effective ways to reduce WP smoking, WP smokers, public health advocates, and policymakers can start responding to the WP epidemic among young people in Florida and the US. Applying HWLs on cigarette packages was effective in reducing cigarettes smoking and its related health risk (Noar 2016, a). Similarly, adopting HWLs for the WP promises to impact smokers, and reduce WP smoking-related morbidity and mortality. This pioneering project will generate pictorial HWLs for the WP developed with the involvement of the target population, and tested on a variety of important policy/regulatory outcomes (e.g., harm perception, intention to quit, exposure to toxicants). Findings from this project will help advocate for the adoption of WP-specific HWLs and disseminate knowledge about WP harmful effects to young people in Florida and nationally.

Specific Aims: 2,081/2,100 characters

Our Team developed 12 pictorial Health Warning Labels (HWLs) for the waterpipe (WP) corresponding to 4 themes; health risks/addiction, harm to others, specific harm, and harm compared to cigarettes. We will build on this work to advance HWLs policies and disseminate knowledge about WP harmful effects to young people in Florida and nationally through the following specific aims:

1. **Adapt the HWLs to young adults in Florida using focus groups.** We will conduct mixed-gender focus groups combined with brief survey with regular WP smokers (6-8 groups; n ≈ 65; age 18-29 yrs) to 1- adapt the 12 HWLs to our target population, 2- explore their optimal placement and size, and 3- select the top 4 HWLs for testing (Aim 2).
2. **Test the top 4 HWLs in a clinical lab experiment.** Using the top 4 HWLs on the device, we will recruit 2 groups of WP smokers (n= 248; age 18-29 yrs) based on their use frequency (beginners, established) for a within- (HWL vs no-HWL; pre- vs post- smoking) and between-subject (beginner vs. established; 4 HWLs) experiment. Participants will be randomly assigned to one of the 4 HWLs conditions and undergo 2 smoking sessions that differ by HWL (HWL vs. no-HWL), with pre-post smoking assessment of harm perception, intention to quit, and toxicant exposure. Participants will receive a follow-up phone call 3-month after exposure to assess longer-term changes in quit attitude and behavior. *We hypothesize* that applying pictorial HWLs to the WP device will; 1- significantly increase harm perception and intention to quit, and reduce puffing behavior, satisfaction, and exposure to toxicants compared to no-HWL; 2- this effect will be more pronounced in beginner than established smokers.
3. **Disseminate knowledge.** We will partner with *Golin, Tobacco-Free Workgroup, and Truth Initiative* to advocate for the adoption of HWLs policies and disseminate knowledge about WP harmful effects to young people in Florida and nationally.

Impact: Communicating WP risks through HWLs promises to reduce WP use and WP-related morbidly and mortality among young adults in the US.

Research Strategy (68,000 characters) 69,450

A. SIGNIFICANCE

This application is a resubmission. We thank the reviewers for their constructive comments and positive evaluation of our application. It was encouraging that the reviewers identified several strengths and the overall value of our proposal and gave it an "Outstanding" total impact score of "2". We equally recognize our application shortcomings identified by the reviewers and tried our best to respond to them thoroughly in this resubmission. Our response letter provides a summary of changes made (pls. see response letter), while the revisions introduced in the proposal are marked by italics.

In the WP commonly used today, charcoal-heated air passes through the tobacco mixture to generate smoke that passes through water on its way to the smoker (Figure 1). Multiple surveillance data from Florida, show that WP smoking has become one of the leading tobacco use methods among youth. This dramatic rise of WP is amplified by the mounting evidence of its addictive and harmful nature, as well as the lag of policy response to it (Gathuru 2015, Sutfin 2017). Evidence suggests that WP smoking is associated with increased risk of lung cancer, and major cardio-pulmonary diseases (Jawad 2013, El-Zaatari 2015, Waziry 2016). Recognizing the threat of WP to people's health in the US, the FDA has recently extended its regulatory authority under the Tobacco Control Act (TCA) to cover WP products including WP tobacco, device and accessories (FDA 2017). This important development created the need for evidence to guide the implementation of effective policies to reduce WP use in the US.

WP smoking rise among young people in Florida and nationally has been fueled by a widespread misperception of "reduced-harm" compared to cigarettes (Haddad 2015, Maziak 2015, a, Bhatnagar 2019). Given that health warning labels (HWLs) represent a cornerstone strategy to communicate smoking-related risks and reduce tobacco use globally, leading public health authorities consistently recognize the importance WP-specific HWLs as a priority for reducing WP use (FDA 2017). In fact, the first measure adopted by the FDA to control WP smoking was requiring a text HWL on WP tobacco; *"WARNING: This product contains nicotine. Nicotine is an addictive chemical"* (FDA 2017). While a good first step, it is inadequate given: 1- the superior performance of pictorial HWLs over text, 2- the limited contact of WP users with the tobacco package in the popular WP/hookah café, and 3- the established toxic exposures and health effects of WP smoking beyond nicotine (e.g. from charcoal) (Salloum 2016, Sutfin 2017). The long contact with the device itself during a 1-hour average smoking cession moreover, provides a unique opportunity to engage WP smokers with health messages. Therefore, applying pictorial HWLs on the WP device is a promising tool to communicate the risks of WP smoking.

Our project promises to stimulate the implementation of WP-HWLs control in Florida and nationally and provides a model for other states and jurisdictions to consider such interventions to protect their youth. This is consistent with the FDA mandate to establish HWLs on other tobacco products (e.g., WP), which also allows state and local authorities to impose warning requirements other than those on the tobacco product itself (e.g. HWLs on the WP device can be locally legislated) (FDA 2009). Thus, the scientific premise of our proposal are:

1. WP smoking is an important public health problem in Florida.
2. HWLs represent a priority strategy to curb WP smoking.
3. *HWLs are effective in reducing smoking rates and its related morbidity and mortality.*
4. The importance of the device as an optimal placement for WP HWLs.
5. The importance of evidence dissemination to advance WP control in Florida and nationally.

These areas are discussed briefly below.

A.1. WP smoking is an important public health problem in Florida. WP smoking in Florida is increasing dramatically, particularly in youth and young people. Data from the Florida Youth Tobacco Survey show that WP smoking in 2017 has exceeded cigarette smoking and become the No. 2 tobacco use among high school students (only behind e-cigarettes) for ever use (32.1% e-cigarette, 20.4% WP, and 18.6% cigarette) and past-month use (15.7% e-cigarette, 6.2% WP, 4.2% cigarettes) (Florida Department of Health 2018) (Figure 2). Evidence from college students in Florida shows similar trends, where among 1,203 students at the University of Florida, WP smoking exceeded cigarette smoking for ever (46.4% vs. 42.1%) and past-year use (28.4% vs. 19.6%) (Barnett 2013). Evidence from 1,539 students (18-23 yrs.) at the University of Tampa shows that ever WP use reached 64%, a third of whom (34%) were current WP smokers (Martinasek 2016). WP smoking carries similar, or potentially more health risks than cigarettes, due to the added contribution of charcoal (e.g. carcinogens), device and accessories (e.g. infectious disease) (CDC 2018). WP use leads to nicotine addiction, and increases the risk of cancer, chronic diseases, and exposure to secondhand smoke (American Lung Association 2007, Waziry 2016, Awan 2017). More worrisome is the evidence that WP smoking can roll back successes achieved in tobacco control by providing a gateway to cigarettes smoking among youth (Soneji 2015). Thus, WP smoking has rapidly become a public health problem among young people in Florida and requires urgent evidence-based solutions.

A.2. HWLs represent a priority strategy to curb WP smoking. Partially attributed to the "filtering" effect of passing smoke through water**,** many consider WP smoking to be a safer alternative to cigarettes (Haddad 2015). Studies among college students in Florida show that compared to cigarettes, WP smokers have positive perceptions about it, and that these favorable perceptions were predicting future WP use in longitudinal studies (Sidani 2013, Castañeda 2016, Barnett 2017). Therefore, communicating the health risks of WP smoking to young people represents an important avenue for WP control (Cornacchione 2016, Lopez 2017). Applying HWLs on cigarettes packages was effective in raising awareness about smoking harms, preventing initiation and encouraging smoking cessation (Brewer 2016, Noar 2016, b). However, similar evidence regarding the effect of HWLs on WP smoking is still lacking. Given that HWLs represent a cornerstone strategy to communicate smoking-related risks and reduce tobacco use globally, leading public health authorities and scientists consistently recognized HWLs as a priority strategy to reduce WP smoking (Salloum 2016, FDA 2017).

A.3. HWLs are effective in reducing smoking rates and smoking-related morbidity and mortality. *Studies have shown consistently that HWLs are associated with a decrease in smoking rates and smoking-related morbidity and mortality. For example, adopting HWLs policy on cigarette packages in Canada resulted in 12-20% reduction in smoking prevalence and nearly 5,000 fewer smoking-related deaths annually (Azagba 2012, Huang 2014). Similarly, implementing HWLs policy in 1998 in Ireland and Netherlands resulted in almost 464,493 fewer smoking-related deaths by 2010 (Nagelhout 2012, Currie 2013). In addition, 25% to 60% of youth in Canada, the United Kingdom, and Australia reported that HWLs helped prevent them from initiating smoking (Green 2014). Moreover, HWLs policies are expected to reduce tobacco-related health disparity, as their effect on reducing smoking-related deaths was stronger among lower socio-economic groups in several countries, including the US (Mead 2015, Van Minh 2016). Concerns about the "wear out" of HWLs effect are not substantiated by evidence, which shows that such effect is sustained years after the policy implementation (Van Minh et al., Huang et al. 2014). Even among those who tried to avoid noticing the HWLs, smoking prevalence was reduced by 12% and intention to quit increased 1.5 times 2 years after the policy implementation (Van Minh 2016).*

A.4. The importance of the device as an optimal placement for WP HWLs. WP's multiple-components, limited portability, and intermittent, yet long use sessions (≈1 hour) create a unique product configuration and use-setting that is very different from cigarettes (Salloum 2016, Lopez 2017). A recent review of the challenges facing WP regulation in the US suggests that the current FDA text warning about nicotine on WP tobacco is inadequate given the: 1- limited contact with tobacco packaging in the common WP café setting; 2- established toxic exposures and health effects of WP smoking beyond nicotine (e.g., WP charcoal is a major source of carcinogens); 3- substantial body of evidence showing the superior performance of pictorial HWLs over text ones (Gathuru 2015, Sutfin 2017). Thus, the prolonged contact of consumers with the WP device during an average 1-hour smoking session provides a unique opportunity for extended engagement of consumers with HWLs (Maziak 2019, b). WP café setting represents a unique vector for the WP epidemic among youth (Bahelah 2018, Asfar 2019). For example, WP bars and cafés were reported as a usual place to smoke among 59.1% of men and 72.6% of women (18-24 years) in the US (Salloum 2017). Consumers in the WP café setting are usually not in contact with the tobacco packaging, where HWLs are usually positioned (Salloum 2017). A recent qualitative study in Egypt suggests that placing HWLs on the WP devices might increase salience, prevent initiation or trigger quit attempts (Mostafa 2018).

A.5. The importance of evidence dissemination to advance WP control in Florida and nationally. There has been much debate recently about the "translation gap" between research evidence and their application (Brownson 2018). This is mainly due to researchers focusing on only peer-reviewed publications and scientific conferences to disseminate their research findings. While scientific publications are important, policy/regulatory relevant research needs to go beyond these channels to try to induce real change and help translate research evidence into strategies to improve people's health (Bero 1998, Brownson 2017, Brownson 2018). *In this project, we have partnered with health communication specialists and media developers with years of tobacco control experience in Florida (Goline) and nationally (Truth Initiatives) to communicate our research findings to two main end-users; 1- legislators and policymakers, and 2- young people in Florida and nationally.* We have also partnered with a broad scope of public health organizations in Florida to help disseminate our findings and advocate for the implementation of HWLs to curb WP smoking.

Summary: This application is responsive to the dramatic popularity of WP smoking among young people in Florida and the urgent need for evidence-based solutions to help the state respond. *Given the widespread misperception of reduced-harm among WP smokers, the prolonged contact of smokers with the WP device, and the established effect of HWLs on reducing tobacco use and its related morbidity and mortality, communicating WP risks through HWLs on the device represents a promising strategy for WP control. This project will provide tested WP HWLs to advocate for the adoption of WP-specific HWLs policies and disseminate knowledge about WP harmful effects to young people in Florida and nationally.* This pioneering work will likely provide a model for other states to respond to the spread of WP smoking among their youth.

B. INNOVATION

There are two innovative aspects:

B.1. Focusing on the application of HWLs on the device. HWLs are usually placed on the tobacco package (e.g. cigarette pack) (Hammond 2009, a), which is the placement for the current FDA WP text warning. However, given the multi-component nature of WP, and the importance of these components for smokers' experience and exposures (Shihadeh 2005b, Asfar 2019), considering other WP components for the application of HWLs for the WP is needed (Salloum 2016, Salloum 2017). Recently, our team developed a WP-sensitive

framework to guide research into WP policies, emphasizing the importance of other WP components (e.g. device) for the placement of HWLs (Figure 3) (Salloum 2016). While testing all potential placements of HWLs is beyond this study, our decision to test the application of HWLs on the device is innovative and responsive to the unique configuration and use-setting of the WP.

B.2. Using clinical lab methods to test the effect of HWLs on WP smokers, including Exhaled Breath Condensate (EBC) markers of oxidative stress. Clinical lab methods' strength lies in their ability to provide quick and sensitive regulatory-relevant evidence, as the first testing of product modifications before real-life implementation (Breland 2006). However, such methods have not been applied to test the potential of HWLs for WP smokers. In 2016, Maziak received an R01 from FDA/NIDA (R01DA042477) to establish a clinical lab at Florida International University (FIU) and provide the FDA with evidence about the potential of flavor regulation for WP control (Ben Taleb 2018, Ben Taleb 2019, Maziak 2019, a). We will build on this investment to further advance important policy and regulatory avenues for the WP in Florida. Smoking a WP device fitted with HWLs will allow us to assess the effect of HWL on several important outcomes for WP control such as harm perception, intention to quit, puffing behavior, dependence measures (satisfaction, urge to smoke, withdrawal), and toxicant exposure (CO, nicotine, oxidative stress). Moreover, the use of novel and noninvasive EBC technology to look for markers of oxidative stress can provide valuable information about airway insult associated with WP smoking, and whether exposure to HWLs can ameliorate it (Figure 4). We will collect EBC and test it for 6 biomarkers (8-oxodGuo, 8-oxoGuo, 8-isoprostane, formaldehyde, acetaldehyde, and malondialdehyde) that are important for WP smoking (Hunt 2002), and are predictive of long-term respiratory disease (Montuschi 2002).

Summary: The originality of this project stems from its application of novel, WP-sensitive approach to provide pioneer evidence to guide the application of HWLs for WP products in Florida.

C. APPROACH

Despite the need to communicate WP risks to smokers, and the well-established effectiveness of HWLs in tobacco control, there have been no systematic efforts to develop HWLs for the WP (Islam 2016, Salloum 2016). In this proposal, we will apply a theory-guided, mixed-method approach to adapt and test HWLs for the WP. Current recommendations for designing and evaluating HWLs indicate the need to; 1- consider the target population's perception of messages (Hammond 2009, b) in developing the HWL, and 2- to evaluat HWLs using a combination of qualitative evaluation, conducted while the HWLs are being developed, and quantitative evaluation and testing on the target population (Hammond 2008). In this project, we will follow these recommendations to adapt WP-HWLs to our target population of young adults in Florida and test them on policy-important and theory-driven outcomes in a clinical lab experiment. Our approach provides an optimal balance between qualitative assessments (focus groups) needed to get at our target population's (young people in Florida) feedback about the HWLs, to quantitative assessment using experimental lab methods that allow for comprehensive and standardized testing of the developed HWLs. Such theory-driven, experimentally robust approach promises to provide the level of rigorous evidence needed to advance HWLs policy and regulation in Florida, and beyond.

C.1. Preliminary Studies and Investigators.

This project is a collaborative effort between investigators at the University of Miami (UM, Asfar), Florida International University (FIU, Maziak and Bursac), Florida Tobacco-Free Workgroup (Thurer), tobacco control media and advocacy specialist (Abrams; Golin), youth-oriented anti-tobacco campaigns expert (Vallone; Truth Initiative), health communication

specialist from the University of Memphis (Schmidt), and FDA legal advisor (Lindblom). For the past decade, our team has been on the forefront of working together to provide evidence about WP harmful and addictive potential, and to elucidate its complex nature for regulatory/policy purposes. Since the main work of this application involves: 1) using qualitative research methods to develop the HWLs; 2) using clinical lab methods to test these HWLs; and 3) using communication approaches to disseminate research findings and advocate for policy change, below we summarize our experience in these 3 areas.

C.1.1. Experience in applying qualitative methods to develop WP-related interventions. *Asfar, Maziak, and Schmidt are long-time collaborators on NIH funded research and capacity-building efforts to reduce WP smoking internationally. This team applied mixed qualitative and quantitative methods to understand WP smoking patterns and develop WP interventions (Maziak 2009, Asfar 2014, Asfar 2016). Asfar also led a thematic analysis of customers' reviews of WP cafés in the US to identify factors contributing to their popularity. She showed that features related to WP's 3 components; tobacco, device, and charcoal are important for consumers' choice of WP cafés (Asfar 2019). Recently, our team was funded by NIH (R01TW010654) to develop WP-specific HWLs internationally. In this project, Asfar has led the first stage of developing 12 WP-HWLs using a Delphi study approach (Asfar 2019). First, we have developed 28 HWLs corresponding to 4 themes; health risks/addiction, harm to others, WP-specific harm, and WP harm compared to cigarettes. The top-ranked HWLs by an international expert panel in each theme were then selected for the final list of 12 HWLs (Figure 5). These HWLs were then discussed in focus groups in 2 countries (Lebanon, Tunisia) for further adaptation to the target population (Ben Mansour 2019, Nakkash 2019). In this project, we build on this experience to systematically adapt and test these HWLs for young WP smokers in Florida. Schmidt, our public health graphic designer, has led over 60 health communication projects in various media platforms (graphic design, video, photography, animation) (Schmidt 2008, Ullmann 2018). Thus, our team's experience in WP science and in applying qualitative studies to adapt and further develop WP-specific HWLs demonstrate our ability to conduct the proposed Aim1.*

C.1.2. Experience in using clinical lab methods to provide evidence for WP regulation. Our team has pioneered the use of clinical lab methods to the study of WP, and has applied them recently to the study the potential of tobacco flavor regulation for the WP (Maziak 2009, Maziak 2019, a)**.** In preparation for this application, Maziak and Asfar conducted a proof-of-concept pilot study to test the potential effect of HWLs on the device on WP smokers' satisfaction, and exposure to toxins (Maziak 2019, b). We recruited 30 WP smokers, who completed two, 45-minute ad libitum smoking sessions that differed by HWL undivided condition (with vs. without) in a crossover design study. Exhaled carbon monoxide (eCO) was measured before and after each smoking session, and participants completed questionnaires assessing their smoking experiences and perceptions. This pilot study showed that placing HWL on the WP device has the potential to reduce WP smoker's positive experiences, and exposures (e.g. eCO). For example, we found lower levels of eCO following smoking the WP fitted with HWL (17.8 ppm) compared with smoking WP without HWL (24.5 ppm; $P<0.05$) (Figure 6). We will build on this experience by conducting a larger, well-powered, theory-driven study with a comprehensive assessment of change in harm perception and intention to quit, dependence, oxidative stress in EBC, and puffing behavior among young WP smokers in Florida.

C.1.3. Experience in using communication approaches to disseminate research results and advocate for policy change. In the past 2 years, Maziak, Abrams, and Thurer have been collaborating to produce several educational videos about the harmful and addictive profile of WP smoking targeting different audiences (TV Channel 6). These videos have been used by *Tobacco Free Florida* to increase WP smokers and nonsmokers' awareness about WP health

risk. In this application, we will build on this successful collaboration applying a more structured approach to disseminate our project results to wider audiences of policymakers, tobacco control advocates, public health organizations, and young adults. *Vallone, our new collaborator from the Truth Initiative, is currently leading the evaluation of Truth®, one of the largest and most successful youth tobacco prevention campaigns (pls. see letter from Vallone). Vallone will use the messages and images we developed for the HWLs in their counter-tobacco campaigns, and evaluate them for harm perception and quit attitude as part of their standard evaluation (Vallone 2017, a, Vallone 2017, b). Our team also includes Lindblom who served as Director of Office of Policy at FDA-CTP before joining Georgetown as Director of Tobacco Control and Food & Drug Law. Lindblom will guide our team on the legal aspects of applying HWLs to the WP consistent with FDA's deeming rule, its statutory authorities, and state and local governments' constraints (pls. see letter from Lindblom).*

Summary: Our team's work on the WP spans more than a decade of research and theoretical developments using qualitative, quantitative, and clinical lab studies to inform the public and policymakers about WP smoking risks and effective interventions to reduce them. This experience and our leadership in the field of WP science will allow us to conduct the planned studies successfully.

C.2. Conceptual model: For the evaluation of HWLs, we adopted the message impact framework that is based on communication (McGuire 1981, Petty 2018) and health behavior theories (Fishbein 1975), and has been used applied successfully in cigarette HWL research (Noar 2016, a). This model assumes that features of the HWLs will influence behavior through a chain of psychological events including how HWLs will: 1- attract smokers, 2- influence emotion (e.g. attention, fear), 3- affects cognitive reaction such as thinking about the risk (harm perception), then 4- intention to change the behavior (intention to quit), and ultimately 5- change behavior (e.g., reduce or quit smoking) (Figure 7). Our mixed-method approach will allow us to measure these outcomes throughout our proposed research. For example, Aim 1 will allow us to assess communication outcomes mainly (e.g. attention, reaction), while Aim 2 will allow us to measure additionally subjective and objective outcomes such as perceived harm, intention to quit, smoking behavior, and exposures. Applying a robust theoretical model, will allow us to study the effects of HWLs on important policy and regulatory outcomes, and suggest plausible mechanisms of HWLs action to advance HWL research.

C.3. Considerations informing our approach:

C.3.1. Participants. We are targeting young people aged 18-29 yrs, since this age group is particularly vulnerable to WP uptake and progression (Barnett 2017, Kasza 2017, Florida Department of Health 2018). *As some of our outcomes in the lab study are related to nicotine dependence, we will target 2 groups of WP smokers based on their use frequency; beginner, and established smokers. This adds to the complexity of studies, but considering common WP use patterns among our target population and the reviewers' comments, it seemed imperative to assess our outcomes in WP smokers at different stages of their smoking trajectory (Maziak 2019, a). In addition, participants who participated in our previous research (e.g., pilot study) and those who will be recruited in the focus groups study will be excluded from the lab study to avoid contamination.*

C.3.2. HWLs development. Given the ample evidence about the advantage of pictorial (text + image) over text-only HWLs (Hammond 2011, Noar 2016, b), we focused here on developing and testing the potentially most effective pictorial HWLs tailored to young WP users in Florida. Moreover, in the lab study, we are comparing HWLs on the device with no-HWL (control) to compare the suggested intervention with the status quo (no-HWL on the device). For HWLs placement on the device in Aim 2, we will follow FDA's and international recommendations

about HWL size (50% of principal display areas) (USDHHS. 2011, WHO FCTC 2011). Finally, in Aim 2 we are testing multiple (4) HWLs across different health themes to provide several options for HWLs application and rotation (Hammond 2009, a).

C.4. Aim 1: Adapt the 12 HWLs to young WP smokers in Florida using exploratory focus groups (Month 6 Year 1 - Month 6 Year 2). In this aim we will adapt the 12 HWLs that we developed in the Delphi study (Asfar 2019) to our local population of young people in Florida through a 2-phase process; 1) conduct focus groups combined with a brief survey with member from the target population to obtain their feedback about the developed HWLs and how to enhance their design/effects and select the top-rated 4 HWLs from each theme, and 2) adapt and produce the 12 HWLs based on focus groups results to be used for dissemination (Aim 3), while the top-rated 4 HWLs will be tested in Aim 2 (Figure 8).

C.4.1. Phase 1: Conduct focus groups with young WP smokers in Florida. Available evidence emphasizes the importance of considering the target population's perception of HWLs messages (Hammond 2009, b). Therefore, using focus groups combined with a brief survey, this phase will allow us to adapt the 12 HWLs considering factors internal to our target population and WP smoking (e.g., beliefs, harm perception).

Objectives. This study aims to: 1) adapt and enhance the design/effects of the developed 12 HWLs based on the target population's feedback on the HWLs in term of attention (notice, engagement, general design), reaction (fear, believability, avoidance), effect (e.g. harm perception, intention to quit), and improvement (e.g. relatedness to participants, message clarity and synergy with pictorials); *2) explore optimal placement and size of HWLs on each component (tobacco, device, charcoal),* and 3) select the top 4 HWLs (one from each theme) based on participants' rating (Hammond 2011, WHO FCTC 2011).

Participants and recruitment. We will target young adults (age 18-29 years) in Florida who are regular WP smokers defined as smoking WP at least once a week in the past 6 months (Maziak 2016); and are willing to provide informed consent and attend the focus group session as required. Individuals who report smoking cigarettes or other tobacco/nicotine products (e.g., e-cigarettes, pipes, cigars) will be included to increase the generalizability of results given that concurrent tobacco use is common among young WP smokers in the US (Primack 2013, Kasza 2017). We will recruit participants using a combination of online, offline and in-person recruitment methods to ensure successful recruitment (Buller et al., 2012). Offline items such as posters, flyers and study inserts will be posted and distributed on University of Miami and FIU campuses, nearby off-campus locations, and around WP cafés/bars in Miami. Online recruitment will include student listservs, Facebook, and other social media. In-person recruitment will involve handing out flyers and word-of-mouth targeting WP venues in Miami. Recruitment materials will be IRB approved and will have contact information (phone, e-mail) for initial eligibility screening. Interested callers will be screened by phone, and if eligible will be scheduled for a focus group session. *Each participant will be compensated $36 at the end of the focus group session.*

Procedures. We will conduct 6-8 mixed-gender focus groups with regular WP smokers ($n \approx 65$; age 18-29 years). We plan to recruit equal numbers of women and men. Using a grounded theory approach aimed at generating, confirming and modifying theory (Strauss 1990), data will be examined iteratively and data collection will continue until saturation is reached, indicating that no new themes are emerging; i.e. the planned groups' number (6) is tentative. After the focus group discussion, participants will independently complete a brief survey to rate each HWL in term of self-perceived effectiveness. Dr. Asfar, a specialist in qualitative research will moderate the focus group and train a Research Assistant (RA) to help in conducting the focus groups. Open-ended questions and probes will be developed to guide the discussions and

ensure consistency across groups. The moderator guide and the brief survey will be developed by Asfar, Maziak and Schmidt our public health designer.

Interested WP smokers who call the phone number included in the study ad will be screened for eligibility, asked for contact information to confirm their participation and be given directions about the time/place of their focus group. Each session will start with a general discussion on the nature, confidentiality and general interaction mode for the group discussion. After explaining the study and obtaining written informed consent, participants will be provided with a set of forms, including a Baseline Assessment Questionnaire (demographic characteristics, WP smoking history, use of other tobacco products) and a stapled set of Individual Rating Sheets, one for each of the 12 HWLs (3 HWLs in each of the 4 themes) (Survey Instrument Section 1; Focus Groups Tool A, B, C & D). The focus groups discussion will then entail 4 segments of 15-20 min each (1 for each theme). Each segment will start with a PowerPoint presentation of theme-specific HWLs. Then, after viewing each theme's HWLs, a discussion will ensue about participants' reactions to the segment's HWLs in terms of 1- attention (notice, engagement, general design); 2- reaction (fear, believability, avoidance); 3- effect (harm perception, intention to quit); 4- improvement (relatedness to participants, message clarity, language level and synergy with pictorials); *and 5- optimal placement (size and durability of HWLs for each component - tobacco, device, charcoal).* After the discussion, participants will independently complete a rating question for each label by responding to the question "How effective is this HWL overall?" on a 10-point Likert scale (Thrasher 2012).

Analysis. Focus groups sessions will be audio-taped and transcribed verbatim to assist in the coding of themes related to the discussion. Data will be analyzed using Dedoose Software version 5.0.11 (SocioCultural Research Consultants, 2016), which allows hierarchical linkage of codes for clear visualization of data structure. Two team members (Asfar, RA) will independently review transcripts and develop a consensus plan to identify recurring themes and variants. Coding, data reduction, display, and interpretation will be conducted using Creswell's 7-step analysis framework (Creswell 2009). Overlapping themes will be given greater emphasis. All initial codes and categories both within and across groups will be sorted and compared until core categories of recurrent themes emerge as a basis for Grounded Theory (Corbin 2014). In addition to comparing responses within and between groups, we also will evaluate differences in themes according to important participant characteristics, such as gender. To select the top HWL in each theme, we will calculate the sum of the text and picture rating score in terms of overall perceived effectiveness of each of the 3 HWL/theme and select the top-rated one (with the highest score). Thus, while the information from the discussions will give more detailed feedback about important communication domains and suggests further adaptation and improvements, analysis of the rating forms will provide a snapshot of how the HWLs are perceived in term of overall effectiveness and will help to select the top HWL in each theme to be tested in Aim 2.

C.4.2. Phase 2: Optimize and produce the 12 HWL. Guided by focus group results, we will work with our public health designer (Schmidt) to fine-tune the 12 HWLs. The top 4 HWLs that were selected from each themes will then be produced in high quality for testing on the device in Aim 2, while the developed 12 HWLs will be used for dissemination in Aim 3. To determine the optimal layout (size, placement) of the HWLs on the device, we will follow general guidelines (e.g., HWLs should cover 50% of the principal display areas) and use photos of a sample of the developed labels prepared in different sizes and shapes to see how it will fit the WP device (Hammond 2009, b). For example, given the device's cylindrical shape, a round design, or multiple HWLs may be needed to be seen from all sides. A high-resolution photo of each of the top-rated 4 HWLs with the selected size and shape will be printed out as a sticker to be placed on the device for testing in Aim 2.

Impact. This study will generate 12 WP-specific HWLs adapted for young WP smokers in Florida to be used for knowledge dissemination about WP harmful effects (Aim 3), further development and adaptation by other researchers, and testing of the top 4 in Aim 2.

C.5. Aim 2. Test the top 4 HWLs in a clinical lab experiment (Month 6 Year 2 – Month 6 Year 5). Clinical lab methods have long been used to study emerging tobacco products for policy purposes (Breland 2006, Vansickel 2010). Their advantage over other methods lies in providing clear, quick and less biased estimates of the effect of manipulating parameters that are potentially important policy targets (e.g. nicotine, flavor) on smokers' behavior and exposures (Ben Taleb 2018). *Recognizing the limitation of lab studies vs. real-world WP use, such studies have been a mainstay to test the potential of regulatory-relevant product changes (e.g. flavor) (Ben Taleb 2018, Maziak 2019, a). Lab data from WP users moreover, are closely related to real-world use, as shown by a recent systematic review that concluded: "Health warnings based on early controlled laboratory studies were well-founded; if anything the findings suggest a greater exposure risk" (Jawad 2019).*

Maziak has recently received an R01 from NIDA/FDA (R01DA042477) to establish a clinical lab at FIU to study the effect of tobacco flavor manipulation on WP smokers' experiences and behavior, as to guide the FDA of the expected effects of flavor regulation (pls. see FIU Resources) (Maziak 2019, a). In this proposal, we will utilize this lab model to study the effect of HWL manipulation on a myriad of WP smokers' subjective (e.g. dependence, harm perception, intention to quit) and objective outcomes (e.g. puffing behavior, exposure to toxicants). The study will compare the main outcomes described below pre- vs post- WP smoking under HWL vs. no HWL conditions. We will use the 4 HWLs that performed best from each theme in Aim 1 to assess the study's outcomes as discussed below.

Design and Setting. Utilizing clinical lab methods, this aim provides broad testing of the top 4 HWLs on a myriad of WP smokers' subjective and objective outcomes. *We will recruit 2 groups of WP smokers (124 each, total 248; age 18-29 yrs) based on their use frequency (beginners: started WP smoking in the past 6 months, but smoke WP less than weekly; established: smoked at least once a week in the past 6 months) for a 2x2x2x4 within-subject (2: HWL vs no-HWL x 2: pre- vs post- smoking) and between-subject (2: beginner vs established smokers x 4: HWLs) experimental study. Participant in each group (beginner, established smoker) will be randomly assigned to one of the 4 HWLs conditions, and undergo 2 WP smoking sessions that differ by HWL on the WP device (HWL vs. no-HWL), with pre-/post-smoking assessment of harm perception, intention to quit, puffing behavior, satisfaction, urge to smoke, and toxicant exposure (CO, nicotine, oxidative stress) (Figure 9).* We will use Latin Square crossover design balanced for carry-over effect (random order of 4 HWL condition), and to ensure equal distribution of study participants across gender. Accordingly, every subject will undergo 2 WP smoking sessions in the clinical lab setting differing by label (HWL vs. no-HWL) in a balanced random sequence; the same number of subjects gets each label and its order (1st or 2nd session) the same number of times, and for each gender. *As in (Evans 2015, Brewer 2016, Brewer 2019), all participants will receive a follow-up phone call assessment after 3 months of the last session to evaluate the longer-term effect of exposure to the HWLs in real-world setting including HWLs recall, social interactions about WP harms (talk about HWLs with family/friends), and behavioral adaptations in response to exposure to HWLs (e.g., harm perception, quit intention, quitting).*

Such an approach allows:

1- Thorough comparisons without the need for large samples using powerful within-between subjects design.
2- Comparative testing for HWLs with current practice (no label control).
3- Comparative assessment of the 4 HWLs, and the themes they represent, on important

outcomes through between-subjects pre-post analysis.

4- *Assessment of the expected effect of HWLs on WP smokers at different stages of their smoking trajectory.*

Objectives and Hypotheses. To assess WP smokers' responses to the developed pictorial HWLs and inform the state of Florida about HWLs potential to curb WP use among youth in Florida. The study will examine smokers' harm perception, intention to quit, puff topography, satisfaction, dependence, and toxicants exposure (CO, nicotine, EBC oxidative stress) pre-post smoking under 2 conditions (HWL vs. no-HWL). We hypothesize that 1) HWLs on the device will reduce smoking (puffing) intensity, satisfaction, exposure to toxicants, dependence parameters and increase harm perception and intention to quit compared to no-HWL control; *and 2) this effect will be more pronounced in beginning vs. established WP smokers.*

Participants, Recruitment, and Procedures. As in Aim 1, in this study we will recruit WP smokers through the same online, offline and in-person recruitment methods described in section (C.2.2. Recruitment, Aim 1). Individuals who report smoking cigarettes or other tobacco/nicotine products (e.g., e-cigarettes, pipes, cigars) will be included to increase the generalizability of results, as long as they identify themselves as primarily WP tobacco smokers (do not report using cigarettes/e-cigarettes/other tobacco products regularly > 4 times/month). Concurrent regular use of other tobacco/nicotine products would bias the measurement of WP associated outcomes (e.g. dependence measures) (Ben Taleb 2018). *Participants completing the 2 lab sessions and 3-month follow-up will be compensated $36 for each visit. Based on previous experience (Maziak 2019, a), we expect to study 8-10 subjects/month. We will continue recruitment until we reach the target sample (248 with complete sessions). While recruitment is always a challenge, our lab, led by Co-PI Maziak has easily recruited >150 WP users for two-session study (similar design) in the past 2 years with negligible drop out using comparable incentives (Maziak 2019, a). This is due to the widespread of WP smoking among college students in Florida (up to 34%) (Martinasek 2016), especially in a large university with about 57,00 students such as FIU, where our lab is located.*

Inclusion Criteria. Participants need to be generally healthy (at a screening physical examination), between the ages of 21-35 years, willing to provide written informed consent, attend the lab as required, abstain from WP or any tobacco/nicotine for ≥ 12 h prior to study verified by expired air carbon monoxide eCO<5 ppm (Ben Taleb 2018), and use a WP to smoke tobacco in the lab according to study protocol. The 12 hour abstinence period is needed to clear plasma nicotine from prior-to-study smoking (6–8 h after cessation is needed to clear plasma nicotine) (Benowitz 2009) and ensure that all study measures are influenced mainly by study conditions. *Self-reported WP use will be used to define 2 groups of WP smokers (beginners, established), which mostly reflects smokers at different stages of their WP use trajectory (Maziak 2016). These are consistent with common WP use patterns among young people in the US, and our previous lab studies with WP smokers, which will enhance recruitment and generalizability of our results (Primack 2013, Haider 2015).*

Exclusion Criteria. As is standard for clinical lab studies involving smoking, safety concerns require that individuals with self-reported history of chronic disease, psychiatric conditions, history of cardiovascular disease, low or high blood pressure (BP) (systolic BP>150 mm Hg, or diastolic BP>100 mm Hg), seizures, or regular use of prescription medications (other than vitamins or birth control) be excluded (Ben Taleb 2018). Women will be excluded if they are breast-feeding or test positive for pregnancy (by urinalysis) at screening. Individuals who fail the eCO test may be rescheduled at another date.

Sample Size. We built our calculation of the sample size for this study on eCO differences in our HWL pilot study (pls. see preliminary studies C.1.2. and Figure 6), which reported a small-

to-medium effect size (Cohen's f=0.19) depending on HWL condition (Maziak 2019, b). *This study will include 248 WP smokers (124 beginners; 124 established) randomized to 4 groups (62 each) along the 4 tested HWLs. Using repeated measures ANOVA F test with 2 within and 2 between factors, a total sample size of 240 participants will have at least 80% power to detect small-to-medium size effect (Cohen's f=0.2) or larger for 2x2×2×4 within-subject (HWL condition and time) and between-subject (smoking frequency and 4 different HWLs) effects, as well as their interactions at 0.05 level of significance, assuming sphericity and a moderate correlation (0.5) among repeated measures (Cohen 1988). The proposed sample size will provide sufficient power to detect small to medium effects expected based on our pilot data (Maziak 2019, b). It is also feasible as we have not encountered any difficulty in recruiting a large number of WP smokers in our lab studies (Maziak 2019, a).*

Screening, Informed Consent. Individuals who are identified as potentially eligible based on the phone screening will be asked to attend an onsite-screening, which will involve assessment of inclusion/exclusion criteria, physical examination, and urine pregnancy testing for women. Prior to screening, potential participants will undergo a review of the study and consent procedures to ensure that they understand the study, its risks/benefits, and their rights as research participants. Consented (written) individuals will then undergo a physical examination conducted by the research nurse, who will have access to an on-call Medical Monitor (physician) in case of concern or for consultation at any point of the study as it is the standard practice in our lab (Maziak 2019, a, Maziak 2019, b). The physical examination will include measuring BP, heart rate, temperature, pulse oximetry, and weight/height. Successfully consented/screened participants will be scheduled for their 1st session and asked to abstain from all tobacco use 12 hours prior to it.

Experimental Methods. Participants will be randomly assigned to one of the 4 HWLs conditions and attend the lab for two, ~2-h sessions, separated by a 48-h washout period, and differ by HWL on the device (HWL vs. no-HWL control). Session order will be randomly counterbalanced to avoid order effects; counterbalancing also will allow us to study the effect of HWL on smoking behavior prospectively (i.e. between sessions difference is expected to be less when the HWL condition is tested first). *They will also be balanced across the 4 HWLs (62 sessions for each HWL) to allow for equal numbers and robust comparisons of the 4 HWLs and their representative themes.*

At the beginning of the 1st session, participants will provide demographic and personal information including age, socioeconomic status, race/ethnicity, and detailed tobacco use history, especially WP use. Then abstinence will be verified by eCO<5 ppm. Those who have eCO>5 ppm will be rescheduled. Those who are abstinent will get familiarized with the study procedures, measures, and they will be given time to adapt to the lab.

After adaptation, continuous measurement of physiological responses begins, and 10 ml of venous blood is sampled, and participants are asked to respond to subjective measures (pls. see below Outcome Measures). They will then begin a maximum 45 min WP smoking session (time recorded) using a device fitted with the pre-selected HWL or no-HWL according to condition. The HWL will be placed in a constant location/size on the device, which will be placed in front of participant seat (at vision level). For each participant, preferred brand/flavor of WP tobacco (verified at screening) will be used to neutralize the effect of nicotine/flavor on study outcomes. We will follow our tested lab protocol developed to study the WP (Ben Taleb 2018), where prior to each session, the lab staff will pack the WP head with 15 g of the participant's favorite tobacco preparation and cover it with perforated foil. Tobacco will be heated with quick-light charcoal disks (33 mm diameter; 6.2 g; Three Kings, Holland, or similar brand). Initially, a single charcoal disk will be used, and several (pre-weighed) ½ charcoal disks will be made available to the participants so they can add *ad libitum* (Cobb 2012). The timing of each

charcoal application will be noted as in (Shihadeh 2005a). Also for standardization, only one type of WP device will be used. Participants will inhale *ad libitum* and at the end of the smoking period 10 ml of blood will be sampled again, eCO will be measured, and subjective dependence measures (WP satisfaction, urge to smoke, withdrawal) will be assessed as in (Ben Taleb 2018). The session will terminate 30 minutes after the last puff, and the 2nd session will be scheduled. Although it is difficult for a clinical lab environment to perfectly imitate the typical WP social setting (e.g. WP café), we will try our best to make the session area relaxing and entertaining to facilitate natural smoking behavior (e.g., access to fresh magazines, and background music). The same procedure will be conducted in the 2nd session.

Outcome Measures. Outcome measures for this study and the timing of their measurement have been adopted based on our conceptual framework (Noar 2016, a) (Figure 7); their suitability for our study's objectives (Hanson 2009); being validated in studies of health communication and HWLs (Noar 2016, a); and their validated use in clinical lab studies of WP smokers (Ben Taleb 2019, Maziak 2019, a, Maziak 2019, b). These measures are described below (Table 1 & Survey Instrument, Section 2, Lab Study).

1. Harm perception will be asked pre-/post-smoking *and at 3-month assessment* using 1 item "To what extent are you thinking about the serious health effects of WP smoking?" (Thrasher 2012).
2. Intention and motivation to quit will be asked pre-/post-smoking *and at 3-month assessment* using 3 items; "Do you intend to reduce WP smoking?"; "Do you intend to quit WP smoking?", and "How motivated are you to quit WP smoking in the next month?" (Carpenter 2004).
3. *Recall will will be asked at 3-month assessment using 1 item "Try to recall what the HWLs warning information were stated and type it in the box below"(Kees 2010).*
4. *Social interaction will be asked at 3-month assessment using 1 item "Since you started the study, how many times did you have a conversations with your family/friends about the HWLs?" (Brewer 2016).*
5. *Change in WP smoking will be asked at 3-month assessment using 3 items; "Since you started the study, 1- did you stop smoking for 1 day or longer because you were trying to quit WP smoking?, 2- did you avoid smoking WP because you were thinking about the HWLs?, and 3- did you stop WP smoking completely because of the HWLs?" (Brewer 2016).*
6. Toxicant exposure includes eCO, plasma nicotine, and EBC oxidative stress.
   - *e*Co will be measured initially at the beginning of the smoking session (abstinence verification), and within 10 min after the WP smoking session via e-CO monitor (Vitalagraph, Lenexa, KS).
   - Plasma nicotine will be assessed pre-/post-smoking. The research nurse will draw Blood samples (~ 10 ml) via a butterfly needle from a forearm vein before smoking session onset and within 10 minutes of its end. Research staff will centrifuge blood samples and freeze plasma immediately, to be analyzed later by Forensic Chemistry Lab at FIU using Liquid Chromatography Mass Spectrometry.
   - Exhaled Breath Condensate (EBC) will be collected pre-post smoking session to test for markers of oxidative stress and DNA damage. We will test for 6 biomarkers (8-oxodGuo, 8-oxoGuo, 8-isoprostane, formaldehyde, acetaldehyd and malondialdehyde) (Gong 2013, Hu 2015). Samples will be collected during 15 min of tidal breathing through a single-use disposable RTube TM collector (Respiratory Research, Inc., Charlottesville, Va., USA). After sample collection, a plunger will be used to pool the condensed material within the tube into a single sample (about 1.0-2 ml). EBC samples will be divided in aliquots and stored at -80°C. EBC samples will be analyzed by our Forensic Chemistry Lab at FIU using Online Solid-Phase Extraction and Liquid Chromatography Triple Quadrupole Mass Spectrometry (LC-QqQ-MS) and Gas Chromatography Mass Spectrometry (GC-MS) (Hu et al., 2015; Gong et al., 2013). malondialdehyde) (Gong 2013, Hu 2015).

7. Puff topography will be assessed continuously during smoking. It will be measured with a device that was developed by Shihadeh (Shihadeh 2005b), and validated in several WP studies (Maziak 2009, Cobb 2015). Briefly, a pressure transducer is integrated into the WP hose, and inhalation-induced pressure changes are amplified, digitized, and sampled at a rate of 1000 Hz. The software converts signals to airflow (ml/sec) and integrates the flow data, producing measures of puff volume, duration, number, and interpuff interval (IPI).
8. Cardiovascular measures will be assessed continuously during smoking. Two physiological measures will be monitored during each session; heart rate and BP (systolic, diastolic, and mean arterial) using Noninvasive Patient Monitor 507E, Criticare Systems, Waukesha, WI. Physiological data transfer directly to a computer. Heart rate will be recorded every 20 seconds and blood pressure will be measured every 5 minutes before and during WP use.
9. Subjective dependence and satisfaction measures assess smoker's satisfaction with smoking, and the direct effects of tobacco/nicotine consumption on dependence measures (e.g. withdrawal and craving). We will use 4 subjective measures: The Duke Sensory Questionnaire (DSQ) (Malson 2002, Pickworth 2002); The Cigarette/WP Evaluation Scale (WES) (Rose 2000, Malson 2002); The brief version of Questionnaire of Smoking Urges-brief (QSU) (Cox 2001); and Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes 1986). Participants will use a computer keyboard and mouse to respond to these measures periodically in each label condition using Survey Monkey software. The first 2 measures (DSQ, WES) will be used only after smoking, while dependence (QSU, MNWS) measures will be assessed pre-post WP smoking (Ben Taleb 2018, Maziak 2019, b). Subjective measures' assessment will take place within 20 minutes before and after WP smoking.

Statistical Analysis. Prior to analysis, physiological data will be averaged to produce a single baseline value for each measure (10 minutes prior to WP use) and for each 10- minute that a participant was actually using the WP. Topography data will be processed automatically by the topography instrument software to eliminate closely spaced puffs (i.e., IPIs < 300 msec). Such puffs are assumed to be part of the previous puff and the recorded volume and duration values will be added to that preceding puff (Maziak 2009). After this procedure, any puffs less than 5 ml will be considered an artifact and automatically discarded. Remaining data will be averaged for each participant in each condition using all remaining values for puff volume, duration, number, and IPI (Shihadeh 2004). We will address the issue of stability of WP puff topography by correlating topography values across sessions (Shihadeh 2005a). For plasma nicotine, values below the limit of quantitation (LOQ) will be replaced with the value of the LOQ (Maziak 2011). Demographical data will be examined to determine if there are significant between-group differences on measures that may be related to study outcome (some differences are expected due to design such as past 30-day WP use) though these are expected to be minimized as a virtue of randomization. Unexpected between-group differences will be considered as potential adjustment covariates in the primary analysis (Evans 2006). *The primary analysis of each outcome will involve a 4-factor analysis of variance (or covariance) with two within-subject factors; HWL (HWL vs. no-HWL/control) and time (pre-post smoking), and two between-subject factors; smoking frequency (beginner vs. established WP smokers) and HWL (4 group assignment). This approach will be extended into mixed-effects linear regression model in order to adjust for potential confounders such as gender, education, race, SES, and self-efficacy. To assess if gender has any effect on the results, it will be considered as a covariate and we will test the pre-planned interaction with it to determine heterogeneity of HWL by gender as well as potential differential effects.* We will test for carry over effect statistically and will control for it when testing for the primary factors (Senn 2002). Significance levels will be adjusted for violations of the sphericity assumption using Huynh-Feldt corrections (Keppel 1991). The mean square error terms for the overall interaction will be used to conduct Tukey's honestly significant difference test (Keppel 1991), with comparisons at $P < 0.05$ considered significant.

Impact. This study will provide robust testing of the HWLs, and their themes, on a variety of outcomes that are important to assess the potential of HWLs on WP use and popularity among young people in Florida. It will also provide tested HWLs for further dissemination and implementation within the state and nationally.

C.6. Aim 3: Communicate the knowledge obtained to advance WP control in Florida and nationally (Year 1 - 5). *Concerns about our dissemination strategy and its target audience and outcomes necessitate clarifying that the main audiences for our proposed work are policymakers, regulators, and policy advocates, while young WP users are the ultimate target population when the HWLs are implemented. For this purpose, our partnership with Golin is optimal as they have extensive experience in advocacy for public health policy through their work with the Florida Dep. Health, CDC, and others. Still, in response to the review, we now expanded our dissemination to include young adults in collaboration with Truth Initiative, which has extensive experience in tobacco control advocacy focusing on youth. Truth Initiative will use the messages and images we developed in their counter-tobacco campaigns, and evaluate them for further message development and fine-tuning (e.g. Vallone et al., 2017; Hair et al., 2017). We are also involving FDA staff, such as past policy director at the FDA Center for Tobacco Products to guide our team on the legal aspects of applying HWLs to the WP.*

We will apply the Dissemination Planning Tool Steps (Figure 10) to disseminate information about WP detrimental effects and advocate for policy solutions such as HWLs (Carpenter 2005). This Tool was built upon the concept that the process of implementing any research outcome begins with awareness when potential users learn about the products, or findings, and gain some understanding about how they work. The planning tool helps increase this awareness in a systematic way by combining the constructs of diffusion and dissemination (Carpenter 2005). Diffusion is defined as a passive process by which an innovation is communicated through channels over time in a social system (Rogers 2010). Dissemination involves a more active, tailored process of communication, with a goal of persuading users to adopt the innovation (Lomas 1993). Alone, neither construct offers sufficient guidance for successful dissemination of research results; together, the ideas complement and support each other. Both constructs are embodied in the development of this planning tool to guide the dissemination of research results. The Model has 6 elements: 1- research findings, 2- end users, 3- dissemination partners, 4- communication channels, 5- evaluation, and 6- work plan. Our team of communication scientists and professionals with years of experience in tobacco control will apply this framework to disseminate our findings and promote policy solutions for the WP epidemic as follows.

1. Research Findings (What is going to be disseminated?): The research findings are the highlight of our overall effort, but we will also seek to generate newsworthy episodes across the five-year project. Specifically, we will seek to disseminate information regarding the grant and its scope, the final warning labels to be tested, a preview of overall findings, and lastly the formal, official findings of the study.

2. End Users (Who will apply it in practice?): We identified two primary audiences for the information generated by our project:

- *Policymakers: Include those who will be considering the social impacts of the research findings, shaping public opinion, and determining policy interventions. These include state and local legislators, tobacco control and public health leaders, FDA staff, community leaders, and institutional leaders (e.g., superintendents, local health departments, public health administrators where WP venues proliferate).*
- *Young adults and the public: Within this audience, groups that have a high level of interest in this topic can include, collage and high school students and faculty, parents and*

parental groups (e.g., Parent Teacher Association), and medical professionals (e.g., nurses, pediatricians).

3. Dissemination Partners (individuals, organizations or networks through whom we can reach end-users): Our primary dissemination partners will be stakeholders in the tobacco control and prevention community, the larger public health industry, and tobacco control advocacy groups in the state of Florida, including the county-level Tobacco-Free Workgroup and SWAT (pls. see letter from Dr. Thurer, Tobacco-Free Workgroup; Ms. Soto, Consortium For A Healthier Miami-Dade; and Dr. Kobetz, Community Outreach Core at Sylvester Comprehensive Cancer Center; Ms. Rodas, Campaign for Tobacco-free Kids), Tobacco Free Florida grantees, through which public-facing awareness efforts (publicity and communications) will be launched and where implications for local policy change can be considered. The secondary dissemination partners are influential community leaders in Florida, particularly individuals and groups with an interest in public health and tobacco control issues related to youth and young adults, who can shape public opinion and support policy interventions. These would include tobacco control advocates, university and secondary school faculty, health foundation leaders, news editorial figures, among others.

4. Communication Channels (How to convey the research outcomes?). We will use 3 specific channels for promoting the research findings and increase awareness about harms associated with WP smoking: a) the news media; b) partner outreach and mobilization; and c) social and digital media.

- The news media: The news media effort will start with a media announcement, likely in Tallahassee, as the state capital boasts a large Capital Press Corps that influences media coverage statewide. The announcement would be broadcast live via digital and social media to local news and stakeholders in key markets throughout the state (e.g. Miami/Ft. Lauderdale, Orlando, Tampa, Jacksonville, Palm Beach, Naples/Ft. Myers, Gainesville, Tallahassee, Daytona, Panama City and Mobile, AL). We will recommend a “panel-style” format with representatives from three organizations signifying the various aspects of the research and advocacy including SCIENCE (UM, FIU); SOCIAL IMPACTS (our dissemination partners), and POLICY (e.g., Tobacco-free Kids). This group would be complemented with representatives of the “affected class” of the research, like a student from SWAT, a parent, or a former “hookah lounge” employee. All attendees will be prepared in advance with media training, a mock run-through, key messages, and proof points. The event will be coordinated by our agency partner, Golin, who handles such events for the Florida Department of Health, The U.S. CDC, and the U.S. Office of the Surgeon General, among others.
- Partners’ outreach and mobilization: A toolkit will be created by the research teams and their organizations along with partners so that they may best leverage the findings to advance the cause of WP control at all levels. We will work also with partners and advocates to write "opposite the editorial page" (Op-Eds) and Letters to the Editor to frame the discussion among policymakers and influential stakeholders (e.g. The Miami Herald, The Tallahassee Democrat, etc.). Promotional assets in print, digital, video, static, infographic and partner materials will be produced in advance and made available. We will work closely with Tobacco Free Florida to further disseminate this information to stakeholders and partners in the tobacco control movement and plan a preview meeting a week in advance of the announcement to engage and motivate stakeholders.
- Social and digital media: Following the announcement, a digital engagement effort will begin that features key findings of the research and a call-to-action (CTA). The CTA will direct the public to a micro-website that will contain further information and refer to

additional resources. This will also allow us to track and continue to engage our target audiences.

5. *Evaluation (How to determine what worked?). As part of our evaluation of our dissemination efforts, Golin will provide annual recap reports, ad hoc reports for media announcements, as well as a major ad-hoc launch report 30 days after the announcement of the major findings (e.g., Tallahassee event). The reports will capture:*

- *News, digital and social media coverage analysis including impressions, reach, and message pull through. Golin will collect news coverage data and provide details about impressions and reach. Our team will then review each story and count the number of campaign messages that appear in the stories and where it appears to adopt messages with high reach and coverage.*
- *Partner mobilization analysis including engagement and action by partners. Using appropriate tools (e.g. Facebook, Twitter ads, YouTube), Golin will identify posts by partners and report back those that have used campaign assets for more targeted messaging and partner mobilization.*

Golin will also provide key performance indicators (KPIs) to the investigators for evaluation. These KPIs include impressions and reach of materials, engagement with social media content, number of people who have shared content online, social conversations, the number of times video/images have been viewed, and the number of times people have visited a campaign website after seeing/receiving campaign materials. To provide a benchmark for comparison, we will use KPIs from two recent campaigns conducted by Golin (e.g. Tobacco Free Florida Week eEpidemic and/or the Florida Clean Indoor Air Act vaping ban) (Tobacco Free Florida 2015).

In addition, Truth Initiative will use the messages and images we developed in their counter-tobacco campaigns, and evaluate them for further message development and fine-tuning. Truth Initiative has standard and extensive evaluation process for their campaigns (e.g. Vallone et al., 2017; Hair et al., 2017). This process briefly involves three types of studies: Formative, Implementation and Outcome. Findings are continuously used to inform the process so that changes can be made in real-time help ensure campaign success (e.g. Hair et al., 2018).

6. Work plan. Timing of various publications will dictate the release tactics, but generally, important announcements will be supported with a rigorous public relations launch and an engagement strategy that activates partners. When releasing scientific data, it is important to include timeliness of the news (through a media event), and a hook to current events. This process will be timed and repeated ahead of major policy pushes at all stages of the proposed project and will be supplemented with various related activities.

Impact. As we have adopted a complementary approach for the development and testing of HWLs, each Aim feeds into the other, while also serving as a standalone study that will facilitate timely communication of our research findings to a variety of researchers, stakeholders, and policymakers involved in tobacco control in Florida. For example, the HWLs arising from our focus groups study (Aim 1) can be used by other researchers for further development and testing, while their messages and pictorials can be used within campaigns to increase young people in Florida awareness about the harms of WP smoking. Thus throughout the project we will produce and distribute toolkits, messaging, template social media assets, newsletters, and more (Table 2).

C.7. Potential challenges and their solutions

Long term effects of HWLs on smoking behavior is an important parameter that is rarely addressed in the HWLs literature (Noar 2016, a). However, given the complexity and limited portability of WP compared to cigarette pack, which complicates the assessment of HWLs on

smokers' behavior prospectively, we opted to study the effect of HWLs on smokers' behavior in a lab model (Aim 2). Thus, our proposed lab study provides a reliable method of gauging HWLs' short-term potential on WP smokers in the form they will be delivered in the real world. *Importantly, our planned short-term outcomes (e.g. reaction, harm perception, quit intention) have been shown to be strongly correlated with long terms outcomes of cessation (Borland 2009, Fathelrahman 2009, Li 2012). Still, to gauge the potential of HWLs, we have now added a 3-month follow-up assessment to evaluate longer-term recall, social interactions, and behavioral adaptations as a result of exposure to the HWLs (e.g., quitting and quit intention)(Brewer 2016).*

D. STUDY TIMELINE

The total duration of this project is 5 years. During the first 6 months (Mon), we will hire and train study personnel, prepare study protocols and instruments, and obtain IRB approvals. Aim 1, will take place over the following 12 Mon (6 Mon for conducting focus groups, 3 Mon for focus groups analysis, and 3 Mon for optimizing and producing the new HWLs). Aim 2 (the lab study) starts in Year 2, Mon 6 and will continue over the following 36 months until the middle of Year 5. Aim 3 (dissemination) will start in Year 1, and continue throughout the grant's 5 years. The final 6 Mon of the grant will be devoted to data analysis and reporting, although we will expect continuous analysis and reporting of data throughout the grant's 5 years (Table 3).

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