

CIGARILLO WARNINGS IMAGE SORTING EXPERIMENT

Protocol Version Number: 1.5

Protocol Version Date: 1.5, December 2024

ClinicalTrials.gov number: NCT05838378

Funding Mechanism: National Cancer Institute, R01CA260460

Principal Investigator: Jennifer Ross

Phone: 617-358-1905

E-mail: jjross@bu.edu

Statistical Analysis Plan – pages 21-22

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Summary of Changes:

Version	Date	Description of Change	Brief Rationale
1.1	9/7/23	Throughout all relevant sections, changed study process from a 6 week study with a 1 month follow up (“Week 10”) to a 4 week study. [Protocol summary; Background; rationale & purpose; Outcome measures; study design; study procedures; statistical methods]	This change was made based on changes in feasibility with Qualtrics and panel vendor, as well as conversations with the program officer at NIH. This does not change the scope of the study (or statistical power) and still allows us to achieve the aims of the study.
1.1	9/29/23	Revised Schedule of Events in Appendix	To reflect changes to study process/length.
1.1	9/29/23	Added additional information and rationale for study purpose and design, including use of deception. [3.1, 3.2, 4.1]	Changes reflect requests from IRB and discussions with CRRO to justify our study design
1.1	9/29/23	Added additional information about Qualtrics Research Services, including their role in the study [3.1], recruitment & screener [9.1, 10];	Clarify role and responsibilities of Qualtrics for this project.

		privacy and confidentiality [14.1, 14.2]	
1.1	9/29/23	Added additional details about the incentive process [9.1.2]	Additional clarity needed; response to IRB review.
1.1	9/29/23	Added details about the potential different recruitment phases depending on feasibility, and how the second phase changes privacy/collection of identifiable information; [3.1; 9.1; 14.1, 14.2]	This was added to address changes in feasibility with Qualtrics to ensure we reach our desired sample size with a hard-to-reach population.
1.1	10/2/23	Clarified study screener and Qualtrics' role.	Clarification needed from IRB review.
1.1	10/2/23	Consent [11]: deleted "assent"; changed from 'at least 18' to 'at least 21'.	IRB review requests; no participants under 18 in study; participants all 21+ for study inclusion.
1.1	10/2/23	Safety review [13]-deleted sample size as a protocol deviation. Updated/increased sample size throughout application from 500 to 600 to align with our desired sample size.	IRB review request.
1.1	10/2/23	Clarified inclusion criteria measure for cigarillo use.	IRB comment/question clarification.
1.1	10/2/23	Revised privacy and confidentiality to discuss possibility of collecting email addresses, when it would happen, and when data would be destroyed [3.1., 14]	Reflects changes in study feasibility and the possibility for phased recruitment and needing to collect email addresses in a later study phase if needed.
1.1	10/2/23	Change survey lengths for each wave.	Changes made to align with other documents, including consent and IRB application.
1.1	10/2/23	Clarified potential benefit [6.2] to align with changes to consent form—that answering questions about their tobacco use may make them think about their tobacco use and stopping.	Alignment with consent form; IRB review comment.
1.1	10/5/23	Section 3.1: further clarified importance of sample of	Additional justification for study design.

		Black/African Americans given history of predatory marketing by tobacco industry, further contributing to tobacco disparities.	
1.1	10/5/23	Revised 3.1 and 12 procedure sections to align with survey items.	Ensure accuracy and alignment with revised study surveys.
1.2	11/12/23	Revised 3.1, 3.2, 6.1, 9, 9.1.2, 12 to clarify opt out and incentives	Additional clarity needed; response to IRB review.
1.2	12/12/23	Deleted previously added sections/content from version 1.1 regarding 'phase 2 recruitment' and possibility of collecting email addresses. This information was deleted from 6.1, 9.1.1, 14.1, 14.2.	Feasibility changed so that we no longer need a phased approach to recruit our desired sample size. Thus, no identifying information is needed to be collected.
1.2	12/12/23	Clarified that our estimated final sample size includes those who may opt out of the study after the Week 4 debrief. Thus, our final analytic sample size may be smaller. Sections 3.1, 9.1.2	Additional clarity needed; response to IRB review.
1.2	12/12/23	Clarified that oversampling for those identifying as Black/African American may be dependent on feasibility at the time the study goes into the field.	Additional clarity needed; response to IRB comment.
1.2	12/12/23	Added text specifying that we will retain and use data from participants lost to follow. Sections 3.1, 8, 9.1.2	Response to IRB comment.
1.2	12/15/23	Updated Schedule of Events to account for Debrief for those who did not participate in Week 4 survey.	Additional clarity needed for debriefing for those lost to follow up or withdrawn.
1.3	10/09/24	Separated screener and baseline surveys. <u>Sections: 9.1.1., 9.1.2., 10, 12, 18: Appendix.</u>	This change was made based on changes in feasibility with panel vendor. This does not change the scope of the study (or statistical power) and still allows us to achieve the aims of the study. This allows us to leave the screener open to recruit as many participants as

			possible within one week, and then have all participants stay on the same study timeline.
1.3	10/09/24	Updated the incentive. <u>Section: 3.1</u>	This change was made based on additional clarifications and feasibility with panel vendor. This does not change the scope of the study (or statistical power) and still allows us to achieve the aims of the study.
1.3	10/09/24	Removed the sentence “ <i>Outcomes measured only at the one-month follow-up will be analyzed using standard linear and logistic regression models</i> ” from <u>Section 15.3</u> because we will no longer have outcomes measured at follow-up.	This was something left in the protocol accidentally after the study design had been changed; this one month follow up had been removed prior to IRB submission. This does not change the scope of the study (or statistical power) and still allows us to achieve the aims of the study.
1.3	10/9/24	Updated debriefing procedure: resources for additional information and final debrief for those not completing Week 4, section 3.1, section 12.	This was revised to address issues within the survey vendor platform to ensure participants received information about the harms of cigarillos and are able to submit the survey; and additional clarity for how the debrief will occur with this vendor.
1.4	12/4/24	Updated the language regarding subject payments. Section 3.1, section 9.1.2.	Response to IRB comment
1.5	12/9/2024	Updated the language regarding subject payments. Section 3.1, section 9.1.2.	Response to IRB comment
1.5	12/9/2024	Updated the sample size. Section 2, Section 3.1, section 9.1.2.	Response to IRB comment

TABLE OF CONTENTS

1	List of Abbreviations	6
2	Protocol Summary	6
3	Background/Rationale & Purpose	6
3.1	Background Information	6
3.2	Rationale and Purpose	9
4	Objectives	11
4.1	Study Objectives	11
4.2	Study Outcome Measures	12
4.2.1	Primary Outcome Measures	12
4.2.2	Secondary Outcome Measures	12
4.2.3	Exploratory Outcome Measures	12
5	Study Design	13
6	Potential Risks and Benefits	14
6.1	Risks	14
6.2	Potential Benefits	15
6.3	Analysis of Risks in Relation to Benefits	15
7	Study Subject Selection	15
7.1	Subject Inclusion Criteria	15
7.2	Subject Exclusion Criteria	15
8	Study Intervention	15
9	Recruitment and Retention Procedures	16
9.1.1	Recruitment Procedures	16
9.1.2	Retention Procedures	17
10	Screening Procedures	17
11	Consent Procedures	17
12	Study Procedures	18
13	Assessment of Safety and Data Safety Monitoring Plan (DSMP)	19
13.1	Definitions for Safety Assessment	19
13.2	Safety Review	19
13.2.1	Multi-Site Safety Monitoring	19
13.3	Reporting Plans	20
13.4	Stopping Rules	20
14	Data Handling and Record Keeping	20
14.1	Confidentiality	20
14.2	Study Documentation, Source Data, and Case Report Forms (CRFs)	20
14.3	Study Records Retention	21
15	Statistical Plan	21
15.1	Study Hypotheses	21
15.2	Sample Size Determination	21
15.3	Statistical Methods	22
16	Ethics/Protection of Human Subjects	22
17	Literature References	22
18	Appendix	25

1 List of Abbreviations

Abbreviation	Abbreviation definition
FDA	Food and Drug Administration
CTP	Center for Tobacco Products, in the FDA

2 Protocol Summary

Title:	Cigarillo Warnings Image Sorting Experiment
Population:	N= 900 young adults (ages 21-35) reporting at least weekly cigarillo use for the last month based on standard measures; males and females; no vulnerable populations will be actively recruited, but pregnant people may choose to participate.
Intervention:	Interventions: longitudinal experiment with an image sorting task (q-sort methodology), participants randomized to one of three warning format conditions, weekly surveys for 4 weeks to complete the image-sorting task.
Objectives:	Assess the relative effectiveness of different warning formats after repeated exposure to warnings.
Design/Methodology:	A between subjects randomized experiment will be conducted via an online survey. Participants will be randomized to one of three warning format conditions (pictorial, Surgeon General text only, FDA text only), and complete weekly image-sorting tasks once a week for 4 weeks where they will view cigarillo packages that have their assigned warning format; they will be asked to categorize the flavors into a priori flavor categories. The goal is to compare the effect of cigarillo warning format on cigarillo quit intentions and behaviors at each weekly assessment.
Total Study Duration:	6 months
Subject Participation Duration:	4 weeks

3 Background/Rationale & Purpose

3.1 Background Information

This Longitudinal Image Sorting Task online survey experiment aims to model a potential cigarillo warning policy to determine the effects of varying cigarillo warning formats on intentions to use cigarillos and cigarillo use behaviors after repeated exposure to the warnings over a 4-week time period among a national sample of young adults who smoke cigarillos.

In the U.S., cigar smoking (including cigarillos) remains a significant public health concern. From 2000 to 2015, consumption of cigars increased 85%, while cigarette consumption decreased 39%.¹ Over 70% of cigar users aged 18-29 report cigarillos as their typical cigar type and 39.4% of young adults have ever used cigarillos.²⁻⁴ Cigarillo use is particularly high among vulnerable populations, including young adults and Black or African American people.^{2,3,5} Cigarillos are marketed by the tobacco industry specifically towards vulnerable populations, including those who are Black/African American.^{6,7} Cigarillo smoke contains toxic chemicals,⁸⁻¹³ and smoking causes significant health consequences, including nicotine

addiction, cancer, heart disease, and lung disease.¹⁴ Negative health effects of consistent cigar use (including cigarillos) result in 9,000 premature deaths and 140,000 years of potential life lost annually, accounting for \$23 billion in lost economic value.¹⁵ However, some young adults erroneously believe that cigarillos are less harmful and less addictive than cigarettes.^{16,17} These misperceptions contribute to cigarillo use.¹⁸⁻²⁰

One approach for conveying the health risks of cigarillo smoking and discouraging use is through warning labels. The Food and Drug Administration (FDA) has regulatory authority over cigarillos and requires the display of six rotating text-only warnings on cigarillo packaging, although these warnings have not been implemented due to litigation. Pack warnings are effective because consumers are exposed to them at multiple points: at the point-of-purchase and prior to each use.^{21,22} We posit that cigarillo warnings could be strengthened by adding images depicting the health consequences of smoking. Data consistently show that pictorial warnings (text warnings that also include an image) for cigarettes are more effective than text-only warnings on several outcomes, including attention to the warning, intent to quit, intent to not initiate, cessation, reducing smoking urges, forgoing cigarettes, and reducing cigarette purchasing behaviors.²³⁻²⁷ However, little is known about the impact of cigarillo warnings on behavior.²⁸

In our previous work (R03CA206487, PI Ross) we developed pictorial cigarillo warnings by pairing images with the six FDA text-only cigar warning statements.²⁹ In an online study with a nationally representative sample, we found that pictorial warnings were more effective at eliciting negative emotional reactions than text-only warnings among young adult cigarillo users and susceptible nonusers.³⁰ They were also perceived as more effective at discouraging future cigarillo use. We now seek to understand the impact of cigarillo warnings on behavior and intentions after repeated exposure. The presence of warnings that communicate about risk can result in negative emotional reactions and cognitions about the harms of smoking. Furthermore, warnings are effective after multiple exposures over time through message repetition.³¹

Evidence is building that pictorial cigarette warnings impact intentions and smoking behavior, particularly after repeated exposure.³² However, few studies (on any tobacco products) have tested the impact of warnings on intentions and behavior after *repeated* exposure to the warning. Most of what is known about the impact of warnings after repeated exposure comes from observational studies, examining changes in smoking behavior after a country implements new pictorial warnings. In a systematic review of observational studies, changes in behavior were observed from either comparing countries that implemented strengthened (including pictorial or increased text size) warnings to a control country without strengthened warnings (e.g., U.S.) or comparing changes from pre- to post-warning implementation. The systematic review found that implementation of strengthened warnings was associated with increased knowledge about the health risks of cigarette smoking and less cigarette smoking and smoking prevalence.³³ However, the authors could not conclude these effects were solely an outcome of warnings, because many countries included in the review implemented pictorial warnings alongside other tobacco control policies. A 2016 NCI Grantee Meeting on the science of pictorial warnings concluded that a challenge of research in this area is identifying ways to expose participants to warnings in a more naturalistic way to reduce demand characteristics.³⁴ The meeting also concluded that this work is especially needed for other combusted tobacco products, like cigarillos, on behavior, to support regulatory decision-making. Examining the impact of cigarillo warnings over time, while reducing demand effects, will better characterize effects of warnings on behavior. See 3.2 for additional details and justification for study design.

In our study, we are working with Qualtrics Research Services. Qualtrics is a leader in survey software, deployment, methodology, and consumer and academic research that maintains access to over 20 online panels across the U.S. Qualtrics provides online samples, and has been doing so for over 10 years, and completed 15,000 projects across 2,500 universities worldwide. They partner with over 20 online sample providers to provide a network of diverse, quality respondents. Thus, Qualtrics does not have a panel themselves, but works with many other online sample providers. These panels are traditional, actively managed, double opt-in market research panels. Participants in these panels have signed up and agreed to participate in surveys through that specific panel. Participants have also agreed to share whatever personal data with that specific panel. This double opt-in process means that respondents submit an initiation registration form requesting to participate in market research studies with that specific panel. The panels then use data from that request to select studies that would best fit that person. All of Qualtrics' panels they work with require this double opt-in process. Qualtrics' methods allow them to identify and obtain samples of hard-to-reach populations for researchers, including that for the current study.

For our study, Qualtrics will program the survey, and will work with identified panels to recruit, screen, and administer/host the survey. An eligibility screener will first be administered (created by our study team). Our final sample of complete responses will be up to 600 cigarillo users, including an attempt to oversample ($N \sim 250$) cigarillo users who identify as Black/African American because of their increased risk for use, which contributes to tobacco use disparities; the feasibility of meeting this oversampling goal is dependent on panel feasibility at the time the study is in the field. The 600 also includes those who may opt-out in participating after the debriefing; due to feasibility issues, we are not expected to obtain a full complete sample larger than 600. However, to ensure a complete sample size of 600 who complete all 4 weekly surveys, we anticipate inviting 900 eligible participants to the study, anticipating some participants may not complete all subsequent surveys (up to 300 participants). Eligibility criteria are listed in Section 7. Surveys will be completed by the ~600 participants weekly for 4 weeks.

The screener survey will ask about age, race/ethnicity, and cigarillo use behaviors to assess inclusion criteria. After screening, and consent of eligible participants is complete, eligible participants will complete additional measures of cigarillo use behavior, including preferred flavors and brand, and baseline assessment of knowledge and beliefs about the harms of cigarillo smoking. We will also assess cigarillo smoking quit intentions, previous quit attempts, and dependence, as well as use of other tobacco products, cannabis, and alcohol. Participants will then be randomly assigned to one of three cigarillo warning conditions: pictorial (developed by the study team in an earlier study), FDA text-only, Surgeon General text-only; within their condition, participants will view one of the six warnings for all four weeks. Participants will complete an image-sorting task based on sorting cigarillos by flavors. We will tell participants that this is a study to understand consumer perceptions of cigarillos (see section 3.2 for additional details and justification). They will sort 18 images of cigarillo packaging, with the warning of their assigned condition on each pack. We will ask them to sort images according to flavor name based on the following flavor categories: fruit (e.g., Grape), alcohol (e.g., Wine) desserts/candy (e.g., Sticky Sweets), mint (e.g., Menthol), color (e.g., Blue Crush), and other. At each weekly assessment (4 weekly assessments), participants will complete the same image-sorting task with a new randomly generated set of 18 images of cigarillo packaging in their assigned condition from the first week. We will also ask participants about their cigarillo use behaviors in the previous week, including number of cigarillos smoked, frequency of butting-out cigarillos, and frequency of foregoing cigarillos, and their cigarillo use intentions. At the end of this Week 1 survey, we will measure demographics not included in

the screener, including sex, gender identity, socioeconomic status, and sexual orientation. During the Week 2 and 3 surveys, participants will respond to items about their cigarillo smoking in the past week, and then complete the image-sorting task. At the Week 4 survey data collection period, after completing the final image sorting task and items assessed in previous weekly follow-ups, we will assess social interactions, thinking about the warnings, and warning recall and recognition (as a measure of attention). We will also assess beliefs and knowledge about the health risks of cigarillo smoking based on the health risks presented in the warning text statements. We will then present the warning within their condition to assess negative affect and cognitive elaboration. Participants will view a debriefing page, including an explanation of the purpose of the study, emphasizing that the study is not promoting the use of cigarillos or any tobacco product, and provide information about the harms of cigarillo smoking, including cessation services information. We will ask participants if they are interested in additional information about cigarillo smoking harms and quitting. Those who select yes will be sent the resources by the panel provider; we will notify the panel provider the ID numbers of those selected they were interested in more information, and the panel provider will send it to participants to ensure anonymity and confidentiality. For participants who did not complete the Week 4 survey (for example, only completed the screener and Weeks 1 and 3), we will send a debrief that includes the same debriefing information and the opportunity to 'opt out' of us using their data after reading about the study purpose. We will retain and use any data from participants who consented to participate in the study but were lost to follow up.

Participants will receive an incentive amount that they agreed to with their panel provider. When participants are invited to take a survey, they are informed what they will be compensated. The compensation amount per participant is the same. At the end of Week 4 (when the survey closes), the study team will review all participant IDs to determine who is eligible for the full incentive. We will then send that list of IDs to the panel, who will then distribute the incentive. Compensation will be provided within one week of the Week 4 survey closing. The incentive is paid to participants directly through the panel. Participants who complete all 4 weekly surveys will receive the full incentive of \$8, which can be redeemed for gift cards of their choice. We chose to provide payment at the end of the study as it is a strategy used by the panel provider and Qualtrics to ensure participant retention. Participants who decide to opt out of us using their data after the debrief will still be paid their incentive. We have indicated this in the debrief text for participants, too.

We will not collect any identifying information.

This study has no more than minimal risks; potential benefits include an increased understanding of the risks associated with cigarillo smoking and taking action to quit using tobacco.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and policies and procedures of the Boston Medical Center and BU Medical Campus Human Research Protection Program.

3.2 Rationale and Purpose

The proposed study will contribute to the evidence base needed to support the rulemaking process and will have a significant public health impact. The FDA's Center for Tobacco Products has an interest in effectively communicating the risks of tobacco products, including cigarillos. However, there is a critical gap in the science on how to inform the public of the risks of cigarillo use. This project aims to address the gap in the knowledge about cigarillo risk communication by providing information on best practices

for cigarillo warnings. Identifying effective cigarillo warnings is important to inform policy and guide research on effectively communicating risk to ultimately decrease use and tobacco-related morbidity and mortality. This study methodology will also address concerns of previous research by reducing demand characteristics of the study by concealing to participants that the purpose of the study is cigarillo warnings, but instead is a study about cigarillo perceptions. Participants will be debriefed at the end of the study (and those who did not complete Week 4 will be sent the debrief). This increases the rigor of the studies for tobacco warnings.

The use of deception/concealing the main study purpose to participants is done to reduce potential demand effects of the study, which has been identified as needed in the literature and by the NIH tobacco community to strengthen studies and our understanding about the effectiveness of warnings on tobacco products. Our goal is to conceal that this study is about testing different warning formats. The image-sorting task, in which participants will classify a variety of cigarillo packages into a priori flavor categories, was selected because cigarillos come in a variety of flavors (several hundred), many with unique or concept flavor names that do not have distinct flavor characteristics (e.g., Blue Crush, Jazz). While we are not interested in participants' perceptions of flavors, this task will allow participants to view the packaging, which will also contain their randomized warning format. Thus, they are exposed to warnings "naturally" (more so than in a forced exposure warning-focused study) as they would be in the real world. Because of concerns about bias in those who enroll and the data obtained, deception is necessary for a scientifically valid and rigorous study design.

The overall goal of this study is to model the impact of a policy through a behavioral intervention. We would never recommend warning labels as a treatment, or in place of currently-approved cessation practices (e.g., counseling, nicotine replacement therapy). Instead, we are testing a potential policy to be implemented at federal, state, or local levels. This type of research, where explicit descriptions of the study conditions is not revealed, is common practice in tobacco research and is done for specific purposes to increase the rigor of the studies. In general, smoking can be felt as a shameful or stigmatized act, so discussing smoking behavior and quitting in the consent form could lead to enrollment bias – such as getting an oversample only of those who are interested in quitting. It can lead to bias in the data - that people will be subconsciously led to answer things in an unnatural state because they've been already primed to think about the impact of warnings on their behavior. We also do not want participants to believe this is a cessation trial, because it is not.

This research would not be able to be completed without this design, because telling participants that this study is about testing different warnings on tobacco products would essentially reveal the study hypothesis. By revealing this, we weaken the internal and external validity of the study. In particular to external validity, this can reduce not only the reproducibility, but also their practical value.³⁵ In this study, we are attempting to mimic warnings policies while reducing demand characteristics to inform possible future tobacco policies that could be implemented by the regulating agency (FDA Center for Tobacco Products). For example, if we told potential participants that we were interested in how warnings could impact their decision to continue smoking or to quit smoking cigarillos, that may bias the sample of who decides to participate in the study or bias responses in the study. We may only end up with people who are interested in changing their smoking behaviors. Additionally, participants who are explicitly aware of the hypothesized connection between warning exposure and number of cigarillos smoked may alter their behavior (or report an alteration) to provide a particular response – to "hurt" or "help" the study.

My previous studies and some other work, funded by NIH, included single time-point studies where we asked participants to view warnings and then respond to them directly in terms of their attitudes, beliefs, and perceptions of cigars and the cigar warnings (as well as other tobacco products).^{30,36-38} These forced exposure studies that tell participants that the study is about warnings, are informative, allowing us to understand participant reactions to the warnings in the abstract, but the current proposed study could further enhance these findings by allowing us to assess the impact of warnings in situ, to get at the effects of a possible warning implementation. Additionally, study findings from this study design would provide stronger support for a policy to ultimately reduce tobacco-related morbidity and mortality; stronger support would lead to better rationale for regulation and withstand litigation from the tobacco industry against the FDA. In fact, a 2016 Grantee Meeting held by the National Cancer Institute recommended additional studies to test tobacco warnings utilizing methods that reduce demand characteristics.³⁴ Thus, the current study increases the rigor of our research and studying a cigar warnings policy, addressing limitations in previous research by engaging in this image-sorting task to reduce demand characteristics. Thus, participants are likely to know this is a study assessing how cigar packaging may influence their perceptions and behaviors, but will not be told explicitly (until debriefing) that we are looking at warnings.

We believe the risks to participation in this study are minimal, and that our use of 'deception' is aimed at providing a better modeling of a warnings policy in the real world. For any potential psychological harm to participants due to the use of deception, we believe that our consent form and expanded debrief will mitigate this possibility.

We hypothesize that participants who are randomized to the pictorial warning condition will report greater intentions to quit smoking cigarillos compared to those in the FDA text-only warning condition and the Surgeon General text-only warning condition. The text-only warnings serve as control conditions for the pictorial warnings. The FDA text-only warnings were proposed by the FDA in 2016, but their implementation was vacated in 2020 by a federal judge, stating that the FDA had not provided evidence that their proposed warnings were more effective than the status quo warnings (Surgeon General text-only). Thus, we will also assess the relative effectiveness between the two text-only conditions. The randomized experimental design allows us to control study exposures, and the longitudinal design allows us to assess the impact of warnings after repeated exposure; much of the existing literature tests warnings within a single survey setting.

4 Objectives

4.1 Study Objectives

The primary objective of the Longitudinal Image Sorting Task online survey experiment is to model a potential strengthened warnings policy to compare the effectiveness of varying cigarillo warning formats on intentions to quit cigarillos after repeated exposure to the warnings over a 4-week period.

The secondary objective is to compare the effectiveness of varying cigarillo warning formats on cigarillo use behavior after repeated exposure to warnings over the 4-week period.

Exploratory objectives are:

1. Compare differences in quit intentions and behaviors across demographic groups (gender identity, racial identity, sexual orientation).
2. Compare differences in quit intentions and behaviors among those who use other tobacco products (such as cigarettes, e-cigarettes) and substances (cannabis use, including blunting).
3. Assess changes from pre- to post-test on a) beliefs and b) knowledge about the harms of cigarillo smoking across study conditions.
4. Compare those who blunt cigarillos with marijuana to those who smoke cigarillos with only tobacco on quit intentions and behaviors, and stratify by study condition.
5. Assess the impact of the study conditions on participants' social interactions during the study period.
6. Assess the impact of study conditions on participants' reactions to the warnings (recall, recognition, negative affect, thinking about the risks).

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

Intentions to quit smoking cigarillos. This is an outcome we are powered to assess in our sample size and is a predictor of behavior.

- Timeframe: assessed weekly at Baseline (Week 1), Weeks 2-4
- Description: Four survey items: how interested participants are in quitting cigarillo smoking in the next 30 days; how likely they are to quit smoking cigarillos in the next 30 days; how much they plan to quit smoking cigarillos in the next 30 days; and how successful they think they would be if they tried to quit smoking cigarillos in the next 30 days. 5-pt response scale (not at all – Extremely)

4.2.2 Secondary Outcome Measures

1. Cigarillo smoking behavior
 - a. Timeframe: assessed weekly at Baseline, Weeks 2-4
 - b. Description: Four survey items with response options of yes/no: in the past week, have you ...1) butted out a cigarillo before you finished because you wanted to smoke less? 2) stopped yourself from smoking a cigarillo because you wanted to smoke less? 3) tried to quit cigarillos completely; 4) tried cutting back on your cigarillo smoking?

4.2.3 Exploratory Outcome Measures

1. Quitting self-efficacy
 - a. Timeframe: assessed weekly at Baseline, Weeks 2-4
 - b. Description: single survey item asking how successful participants think they would be if they tried to quit smoking in the next 30 days (not at all – extremely)
2. Quitting Stages of Change
 - a. Timeframe: assessed weekly at Baseline, Weeks 2-4
 - b. Description: Single survey item and image of a quit ladder, asking participants where they are now on the ladder in regards to cigarillo smoking (1 no thought of quitting – 10 taking action to quit).

3. Warning recall
 1. Time frame: Week 4 survey after last image-sorting task
 2. Description: one survey item asking participants if they noticed any health warnings on the cigarillo packages during the study, with response options of Yes, No, and I'm not sure. Recall is defined as a "Yes" response.
 4. Warning recognition
 - a. Timeframe: Week 4 survey after last image-sorting task
 - b. Description: One survey item asking participants to identify which warning they saw during the study period. Participants will be shown their warning, a warning they did not see, and "I don't know" response options. Selecting the correct warning indicates warning recognition.
 5. Warning reactions
 - a. Timeframe: Week 4 survey after last image sorting task
 - b. Description: four survey items assessing participants' perceptions of the warning for 1) grabbing attention; 2) eliciting disgust/emotions; 3) thinking about the risks; 4) self-reported learning. 5 point response options ranging from 1 = Not at all to 5= very much.
 6. Beliefs
 - a. Timeframe: Baseline, Week 4
 - b. Description: 11 survey items assessing participants' beliefs about the harms associated with cigarillo smoking, such as relative risk to cigarettes, getting cancer, and inhaling harmful chemicals. 5 point response scale (strongly disagree – strongly agree)
 7. Knowledge
 - a. Timeframe: Baseline, Week 4
 - b. Description: 10 survey items assessing participants' knowledge about the harms associated with cigarillo smoking, such as cigarillos being addictive and causing heart disease. 3 response options: True, false, I don't know.
 8. Social interactions
 - a. Timeframe: Week 4
 - b. Description: 3 survey items assessing the frequency in which participants talked to others about the harms of cigarillo smoking, quitting cigarillo smoking, or about the packages in the study. 5 response options (never – 10 or more times).
 9. Warning Relevance
 - a. Timeframe: Week 4 after last image sorting task
 - b. Description: two survey items assessing participants' perceptions about the relevance of the cigarillo warning for those who smoke cigarillos with cannabis (i.e., blunts). 5 response options from 1 = not at all to 5 = very much.
- 5 Study Design
- Study type: Interventional (clinical trial)
 - Allocation: Randomized to one of three study conditions
 - Accepts healthy volunteers
 - Rationale: Using an online, longitudinal experimental design with Qualtrics allows us to obtain a larger sample and avoid collecting personally identifying information. We will be able to assess the effectiveness of different cigarillo warning formats after repeated exposure during the study period. Additionally, the experimental design allows us to control for differences in the warning formats. The image-sorting task allows us to reduce demand effects.
 - Trial Phase: N/A

- Three study groups: participants will complete 4 weekly cigarillo packaging image-sorting tasks where they are assigned to sort cigarillo packages that have either 1) Surgeon General text-only warnings; 2) FDA proposed text-only warnings; 3) Pictorial warnings.
- Planned variation in intervention dose or schedule: Within their assigned condition, participants will view 1 of 6 FDA-proposed warnings for each of the 4 weeks. Dose of intervention naturally increases during each weeks' image-sorting task.
- Summary of methods: An online experimental longitudinal survey with Qualtrics Research Services. Eligible participants will be randomly assigned to one of three cigarillo warning conditions: pictorial (developed by the study team in an earlier study), FDA text-only, Surgeon General text-only. Participants will complete an image-sorting task based on sorting cigarillos by flavors. We will tell participants that this is a study to understand consumer perceptions of cigarillos, and not explicitly state that it is a study about warning labels. They will sort 18 images of cigarillo packages from various brands with the warning of their assigned condition on each pack. We will ask them to sort images according to flavor name based on the following flavor categories: fruit (e.g., Grape), alcohol (e.g., Wine) desserts/candy (e.g., Sticky Sweets), mint (e.g., Menthol), color (e.g., Blue Crush), and other. At each weekly assessment (4 weekly assessments), participants will complete the same image-sorting task with a new randomly generated set of 18 images of cigarillo packaging in their assigned condition from the first week. We will also participants about their cigarillo quit intentions each week, and their cigarillo use behaviors in the previous week, including number of cigarillos smoked, frequency of butting-out cigarillos, and frequency of foregoing cigarillos.

6 Potential Risks and Benefits

6.1 Risks

We anticipate that the risks to participants will be minimal and manageable; we are not collecting highly personal or sensitive data. No private identifiable information will be collected from participants.

Participants in this study have signed up to take surveys through market research panels. Participants in these panels have signed up and agreed to participate in surveys through that specific panel. Participants have also agreed to share whatever personal data with that specific panel. This double opt-in process means that respondents submit an initiation registration form requesting to participate in market research studies with that specific panel. The panels then use data from that request to select studies that would best fit that person. Participants will receive a unique ID that is automatically generated when they click the link to take the baseline survey; Qualtrics will only have access to that ID, which will be automatically sent and linked to the participants' panel; this allows for connection between the participant and their unique ID. The panel will not have any access or ever see any data collected from this study. Qualtrics also does not have access to the participants' profile or personal data through their panel.

Breach of confidentiality is a potential risk; however, this risk is small given that participants will not report identifiable information.

We also believe that the risk of using deception in this study is low; participants are told that we're interested in their perceptions about cigarillos, which is a broad term and could, theoretically, include

warnings. However, we will provide a detailed explanation of the exact study purpose in the debriefing and allow participants to determine if they will allow us to keep their data via an opt-out process.

6.2 Potential Benefits

By taking part in these studies, participants may increase their knowledge of the health risks associated with cigarillo smoking. Answering questions about their tobacco use may also make them think about their tobacco use and consider stopping. Participants may also experience personal satisfaction of knowing they have contributed to a research project aimed at understanding tobacco risk communications.

6.3 Analysis of Risks in Relation to Benefits

Given that the risk to participants is minimal and manageable, the knowledge to be gained has the potential to fill an important research and policy gap. Specifically, scientific findings will advance regulatory science and assist federal, state, and local governments in communicating more effectively with the public, including to both tobacco users and non-users, and those disproportionately affected by tobacco use, thereby impacting public health by reducing initiation of tobacco use and increasing tobacco cessation.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Aged 21-35 years old
- Current cigarillo user—used cigarillos at least one time per week in the past month, based on standard measures as measured in the screener survey.
- Recruited through Qualtrics Research Services

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Non-current cigarillo user
- Less than 21 or greater than 35 years old
- Not recruited through Qualtrics Research Services
- Non-English speaking

8 Study Intervention

Behavioral intervention: Participants will be randomized to a condition where they will view cigarillo warnings that are manipulated based on their study condition: pictorial warnings, FDA text-only warnings, or Surgeon General text-only warnings. Both text-only warnings serve as the control.

Participants will complete an image-sorting task based on sorting cigarillos by flavors. We will conceal the study purpose from participants and tell them that this is a study to understand consumer perceptions of cigarillos. They will sort 18 images of cigarillo packages of various brands with the warning of their assigned condition on each pack. We will ask them to sort images according to flavor name based on the following flavor categories: fruit (e.g., Grape), alcohol (e.g., Wine) desserts/candy (e.g., Sticky Sweets), mint (e.g., Menthol), color (e.g., Blue Crush), and other. At each weekly assessment (4 total), participants will complete the same image-sorting task with a new randomly generated set of 18 images of cigarillo packaging in their assigned condition from the first week. We will also ask participants about their cigarillo use behaviors in the previous week, including number of cigarillos smoked, frequency of butting-out cigarillos, and frequency of foregoing cigarillos, and their cigarillo use intentions, as well as their use of other tobacco products and marijuana. At the Week 4 data collection period, after completing the image sorting task and items assessed in previous weekly surveys, we will assess social interactions and warning recognition and recall (measures of attention). We will also ask questions about knowledge of and beliefs about the health harms depicted in the warnings (Baseline, Week 4). Participants will view a debriefing page, including an explanation of the purpose of the study, emphasizing that the study is not promoting the use of cigarillos or any tobacco product and will include links to cessation services and information about the harms of cigarillo smoking. Participants for whom we only have partial data, in particular that we do not get Week 4 data from, will be sent a debriefing form that includes the debrief information and the opportunity to 'opt out' of us using their data. We will retain any data received from participants who consented and are lost to follow up. Attempts will be made to contact them for subsequent surveys and the debrief.

9 Recruitment and Retention Procedures

9.1.1 Recruitment Procedures

Qualtrics will host the survey, and works with existing panels for recruitment. Qualtrics is a leader in the field of survey software, deployment, methodology, and consumer research, and has completed 15,000 research projects across 2,500 universities. Qualtrics maintains access to over 20 online sample panels across the U.S. Participants are recruited from traditional, actively managed, double-opt-in market research panels. Qualtrics ensures quality checks, such as excluding duplicate participants or those who finish the survey significantly quicker than the median average time for completion.

Participants are invited to surveys from the panel in which they are already a member of (through the double opt-in process). These invitations occur in a variety of ways, including email. Potential study participants will complete an eligibility screener for inclusion into the study. Participants must be ages 21-35 and be current cigarillo users (use cigarillos at least one time per week for the past month). Further, because we are studying cigarillo warnings in the U.S., only those living in the U.S. are eligible. Our goal is to oversample for young adult cigarillo smokers who identify as Black/African American, so Qualtrics will work with the panel provider to target these demographics for invitation to the study screener. Potential participants who meet eligibility requirements will be invited within the next week to complete the full baseline (Week 1) survey, which will take approximately 15 minutes. Participants will be randomized (by Qualtrics online software) to one of three study conditions.

9.1.2 Retention Procedures

Participants will be invited back for a survey for the next four weeks (4 weeks of interventional data collection total). Weeks 2-3 will take approximately 8 minutes; weeks 1 and 4 will take 15 minutes to complete. In each of these 4 surveys, participants will engage in an image-sorting task to be exposed to cigarillo warnings. Participants will receive an incentive for their participation within one week of the Week 4 survey closing. Qualtrics has successfully recruited and retained participants for multiple-wave studies with their panel providers, and employs a variety of techniques to ensure retention, including pre-survey notifications, reminders, and payment at the end of the study period. Qualtrics will provide us with an anticipated minimum final sample size (week 4) of ~600 total completions for all data collection points; however, the amount may be reduced if participants decide to opt-out of us using their data after the week 4 debrief. Further, the total enrollment number may be ~900 total due to over-enrolling to account for possible retention/drop off of subsequent weekly surveys. Participants who do not complete a survey will still be invited to participate in subsequent weekly surveys, [with the exception of Week 1; participants who do not complete Week 1 cannot be invited back because the informed consent process occurs during Week 1.](#) Participants who decide at Week 4 (end of study) to 'opt out' of us using their data after the debrief will also still be paid. We will also work with Qualtrics and the panel provider to implement any additional retention strategies if needed, including increasing incentive structure and a bonus incentive for completion. We will retain any data received from participants who consented and are lost to follow up or who have requested to withdraw from the study. Attempts will be made to contact them for subsequent surveys and the debrief.

10 Screening Procedures

Before enrollment in the study, participants will complete a brief screening survey developed by our study team to assess eligibility; this will be programmed into Qualtrics software and sent to potential participants. Screening will include a short description of the study, followed by a description of cigarillos. Participants will be asked about their use of cigarillos. We will also collect age and race for study inclusion and plans for oversampling those identifying as Black or African American. Eligible participants will be notified that they are eligible (but not told why) and will receive the informed consent form within the next week. Those who are not eligible will also be notified that they are not eligible for the study; they will not be told why they are ineligible. The screener survey is estimated to take less than 5 minutes.

11 Consent Procedures

Participants will read an electronic version of the informed consent form, and will be asked to select a checkbox to confirm their consent. The consent form will explain the study's purpose, potential risks, expected benefits, protection of confidentiality, and time expectations. Contact information for the local IRB and PI (Dr. Ross) will be provided in case the participant has concerns or questions about the study. A waiver of signed consent is requested. This is an online survey and individual participation involves providing voluntary responses to survey questionnaires. The research presents no more than minimal risk of harm to subjects. Consent language will be included in the introduction to the survey and participants will be asked to click a 'next' button to confirm their consent:

ELECTRONIC CONSENT: Please select your choice below.

Selecting “Yes” below and clicking “Next” indicates that:

- you have read the above information
- you voluntarily agree to participate
- you are at least 21 years of age

Do you wish to participate in this research study?

☐ Yes

☐ No

12 Study Procedures

See the Appendix for the schedule of events.

During the Week 1 survey, after consent is complete in the online survey, participants will complete measures of cigarillo use behavior, including preferred flavors and brand, and baseline assessment of knowledge and beliefs about the harms of cigarillo smoking. We will also assess cigarillo smoking quit intentions, previous quit attempts, and dependence, as well as use of other tobacco products, cannabis, and alcohol. Participants will then be randomly assigned to one of three cigarillo warning conditions: pictorial, FDA text-only, Surgeon General text-only. Participants will complete an image-sorting task based on sorting cigarillos by flavors. We will conceal the study purpose from participants and tell them that this is a study to understand consumer perceptions of cigarillo flavors. They will sort 18 images of cigarillo packages of various brands with the warning of their assigned condition on each pack. We will ask them to sort images according to flavor name based on the following flavor categories: fruit (e.g., Grape), alcohol (e.g., Wine) desserts/candy (e.g., Sticky Sweets), mint (e.g., Menthol), color (e.g., Blue Crush), and other. Participants will then complete additional measures of demographics not captured in the screener survey, including sex, gender identity, socioeconomic status, sexual orientation, and state/territory of residence. This baseline survey is estimated to take approximately 15 minutes.

One week later, and for 3 subsequent weeks (1 survey per week; 4 weeks of image sorting task total) participants will complete the same image-sorting task in the online survey with a new randomly generated set of 18 images of cigarillo packaging in their assigned condition from the first week. We will also ask participants about their cigarillo use behaviors in the previous week, including number of cigarillos smoked, frequency of butting-out cigarillos, and frequency of foregoing cigarillos. We will assess their cigarillo use intentions. The weeks 2 and 3 surveys will take approximately 8 minutes to complete.

At the end of data collection period, in addition to completing the final image sorting task and items assessed in previous weekly follow-ups, we will assess social interactions and thinking about the warnings. We will also assess warning recognition and knowledge about the health risks of cigarillo smoking based on the health risks presented in the warning text statements. We will then present their warning and will assess reactions, including affect and thinking about the health risks. This survey will take approximately 15 minutes to complete.

At the end of the final survey, participants will view a debriefing page, including an explanation of the purpose of the study, emphasizing that the study is not promoting the use of cigarillos or any tobacco product and will include information about cessation services and about the harms of cigarillo smoking.

Although we intended to include direct links to smoking cessation resources and information about the health risks of cigarillo smoking, technical limitations prevent embedding such links, as participants would be unable to submit the survey if they clicked on them. Instead, we will offer additional information and resources upon request. This information will be sent separately to participants who did not complete the Week 4 survey, including those who withdrew from the study.

13 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

13.1 Definitions for Safety Assessment

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable occurrence in a human subject, including any breach of confidentiality.

Serious Adverse Event (SAE) is not applicable to this study.

Life-threatening is not applicable to this study.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

13.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows: This study poses no more than minimal risk. We will work with Qualtrics to ensure no breach of confidentiality.

13.2.1 Multi-Site Safety Monitoring

Not applicable.

13.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BU Medical Center IRB in accordance with IRB policies:

- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.

13.4 Stopping Rules

The study has no pre-defined stopping rules.

14 Data Handling and Record Keeping

14.1 Confidentiality

Participants will be granted a study ID automatically generated by Qualtrics that will be used to connect their responses across survey waves. The study ID will be linked to an ID used by their opt-in panel so the panel can appropriately target participants in this study; the panel will not have any access to the study data. The Qualtrics study ID will not be linked to personally identifiable information in the data provided to BU upon completion of the study and is not a searchable identification number outside of the Qualtrics or 3rd-party databases.

In addition to the de-identified data files that will be provided to BU upon completion of the study, Qualtrics maintains survey responses in their data centers. Per Qualtrics: "Qualtrics' database access is restricted and requires authorization. All computer equipment (servers, SANs, switches, routers, etc.) is redundant and is located in secure, environmentally controlled data centers with 24/7 monitoring. Web traffic does not directly access the database and database requests are reversed proxy via an application server to the database. All information is secured via industry standard firewalls and stringent IT security policies and procedures. We utilize industry standard web application firewalls and DDOS protection. Qualtrics also leverages sample partners who are meticulous in their multiple levels of security that include redundant data centers, secure servers, encryption which includes one-way encryptions, numeric IDs, secure .Net platforms, security clearance, industry standard firewalls, 24/7 monitoring data centers, confidentiality agreements, and physical, electronic, and managerial procedures."

Final study results will be shared on ClinicalTrials.gov; the study has already been registered (NCT05838378). PI Ross will work with the BUMC ClinicalTrials.gov Administrator, who she has productively worked over the last several months. She has already been in contact with Dr. Damus to discuss this process. Study findings for primary and secondary outcomes will occur no later than 10 months after final data collection ends.

14.2 Study Documentation, Source Data, and Case Report Forms (CRFs)

All data collected will be primary data collection obtained through working with Qualtrics Research Services panels. They surveys will be collected online, and, thus, directly entered electronically into Qualtrics survey software; there will be no paper copies of data. Data will be obtained from 4 waves of online data collection plus the screener survey. No identifiable information will be collected; only demographic information required for reporting to NIH will be reported individually (age, sex/gender, race, ethnicity) into the NIH Human Subjects Assist Reporting System.

See Section 18 Appendix for the following data collection forms: 4 survey waves.

14.3 Study Records Retention

A waiver of signed informed consent is requested.

15 Statistical Plan

15.1 Study Hypotheses

Primary Objective:

Hypothesis (H_a): Participants randomized to the pictorial warning condition will report greater intentions to quit smoking cigarillos compared to those in the text-only warning conditions (FDA and Surgeon General text-only).

We also hypothesize that participants randomized to the FDA text-only warning condition will report greater intentions to quit smoking cigarillos compared to those in the Surgeon General text-only warning condition.

Null hypothesis (H_0): There will be no significant differences in intentions to quit smoking cigarillos across study conditions.

Secondary Objective

Hypothesis (H_a): Participants randomized to the pictorial warning condition will report butting out cigarillos, stopping cigarillo smoking early, increased quit attempts, and cutting back on cigarillo smoking more than those in the text-only warning conditions (FDA and Surgeon General text-only).

We also hypothesize that participants randomized to the FDA text-only warning condition will report butting out cigarillos, stopping cigarillo smoking early, increased quit attempts, and cutting back on cigarillo smoking compared to those in the Surgeon General text-only warning condition.

Null hypothesis (H_0): There will be no significant differences in cigarillo smoking behavior across study conditions.

15.2 Sample Size Determination

Our sample size justification is based on a 4-week trial of pictorial cigarette warnings and behavioral intentions (Brewer et al.).^{23,39} For our study, a sample size of ~167 participants in each warning condition will be sufficient to detect an average difference of 0.20 units on the behavioral intentions scale between any two warning conditions, assuming a standard deviation of 1.1 units,²³ six weekly measurements with a moderate correlation of $\rho=0.30$, a power of 80%, assuming a two-sided

significance level of 5%, and a two-sample Z-test from a repeated measures analysis.⁴⁰ For a much higher correlation of $\rho=0.60$, the difference detectable between any two conditions increases to 0.26 units. These differences correspond to effect sizes of $d=0.22$ and $d=0.26$, respectively. Subgroup analyses within the Black/African-American population with $n=100$ per condition will be powered to detect effect sizes of $d=0.28$ and $d=0.34$ under the same model assumptions.

15.3 Statistical Methods

Baseline differences between warning conditions will be examined using t-tests for continuous variables and χ^2 tests for categorical variables. Differential attrition will be examined using logistic regression models. Continuous outcomes that are measured weekly, including the primary outcome, cigarillo intentions, will be modeled using random-effects linear regression to account for the correlation among repeated measures, controlling for any variables that differ at baseline between conditions or for which we find differential attrition. Similarly, categorical outcomes will be modeled using random-effects logistic and multinomial regression models. To examine whether warning effects differ by participant characteristics (e.g. race, sex), interactions with condition will be included in a separate analysis. We will also assess whether Black/African-American race moderates the effect of warning condition by including interaction terms between Black/African American race and warning condition. To examine whether any effects of warnings emerged over time, exploratory analyses will include an interaction between time (Week 1-Week 4) and warning condition. If there are no statistically significant differences between the two text-only conditions (FDA text-only, Surgeon General text-only), we will consider collapsing these conditions for data analysis.

16 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston University Medical Campus IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a digital consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is enrolled in the study.

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18 Appendix

Schedule of Events

Cigarillo Warnings Image Sorting Experiment: Schedule of Events

