CONTENTS

SUPPLEMENTARY METHODS

Description of Compliance Incentive Program

Compliance was incentivized using a semi-bogus pipeline. All participants earned five raffle ticket entries at each visit for compliance (3 tickets), honesty about their compliance (1 ticket) and attendance (1 ticket). Participants provided a spot urine at each visit and were told that participants' raffle tickets would only be "validated" if appropriate based on the urine they provided. One drawing was completed each month and prizes ranged from $10–$750. Staff drew winning raffle tickets until a "valid" raffle ticket was drawn.

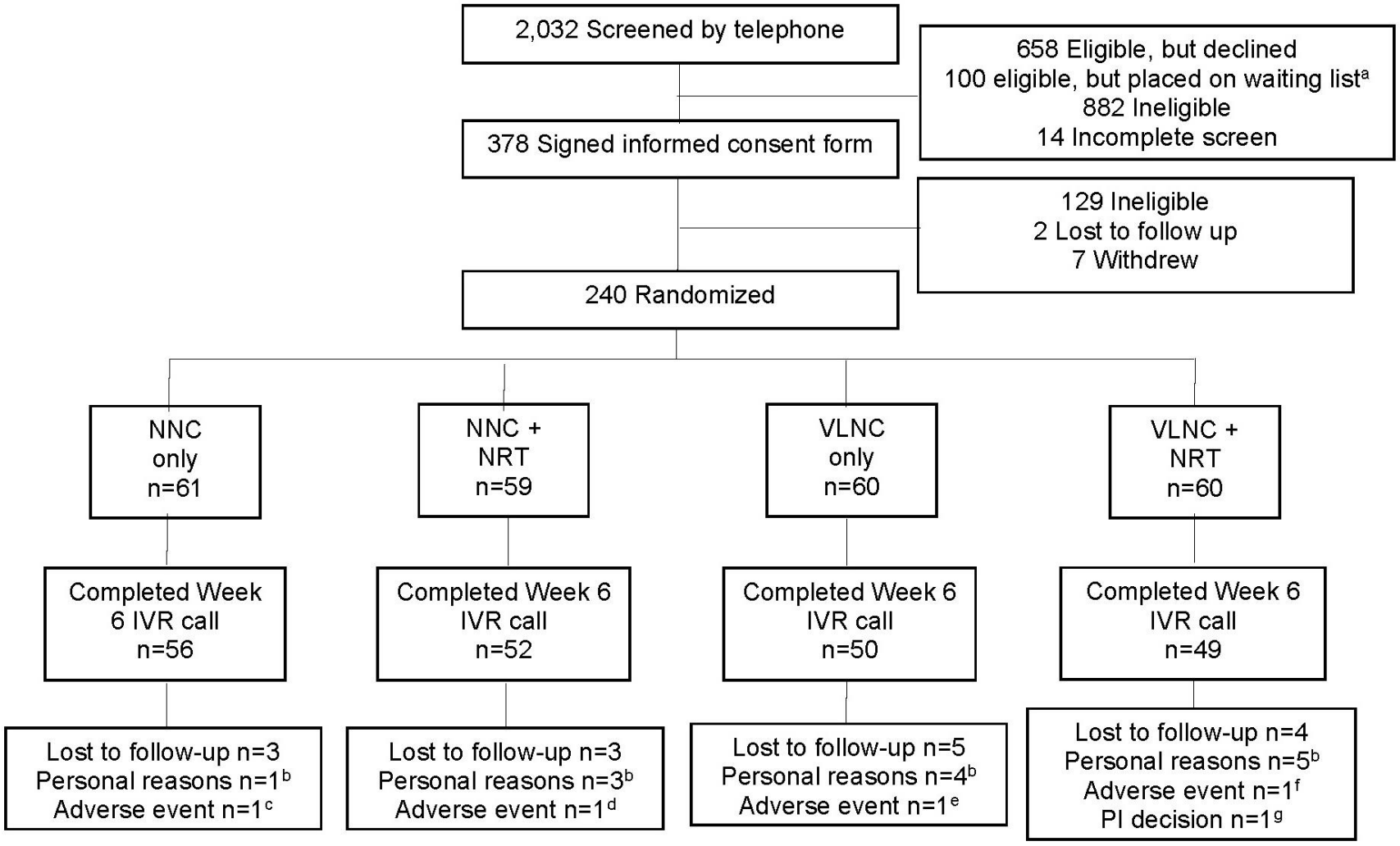
In reality, validation procedures differed for participants assigned to Very Low Nicotine Content (VLNC) and Normal Nicotine Content (NNC) cigarettes. For VLNC participants, urinary anatabine levels were tested each month by the University of Minnesota, and evaluated against criterions of 0.012, 0.016, and 0.02 nmol/ml for 3, 2, and 1 compliance tickets. These criterions were developed using data from a prior study and the intent was to require higher levels of compliance to earn more tickets.[1] Tickets given for honesty were validated when participants reported non-study cigarette use or when they reported compliance and met a urinary anatabine cutoff for compliance (0.012 nmol/ml). Anatabine, a naturally occurring minor alkaloid found in tobacco, was used for assessing compliance because anatabine levels are reduced in the VLNC cigarettes compared to NNC cigarettes[2] and anatabine levels are not impacted by use of the transdermal nicotine patch.[3]

Anatabine cannot correctly classify NNC participants as compliant or not compliant. Thus, although NNC participants were given the same information about the incentive system, in reality their tickets were validated by yoking them to another participant in one of the VLNC groups. This yoking procedure was used rather than simply validating all NNC tickets to ensure equal compensation between NNC and VLNC groups. Thus, for VLNC participants, contingencies of the incentive system were real, but for NNC participants the incentive system was bogus. Because it was possible for participants to win the raffle for a compliance or honesty ticket when they had not been compliant or honest, participants were never told which "ticket type" had been drawn, leaving open the possibility that the winning ticket was for attendance.

Description of Abstinence Incentive Week

During the seventh week of the study, participants were provided with a descending monetary incentive to remain abstinent from smoking each day. Participants assigned to the patch were encouraged to continue wearing their patch during this week. Participants were instructed to continue to use their assigned study cigarette during the abstinence week if they were not able to abstain from smoking. Payment for abstinence decreased each day ($80, $40, $20, $10, $5, $2.50, $0 per day). Abstinence was verified using two expired carbon monoxide (CO) readings each day completed by the participant on their own. Participants were provided with a piCO+ CO monitor and an iPhone to take home. Participants were required to record a video of themselves completing a CO reading each morning and evening, and submit this video via text message to study staff. Each video was reviewed by a study staff member who scored the reading, verified the CO measure was completed by the participant, and provided the participant with feedback about whether their reading met criteria for receiving the incentive. Both readings were required to be less than 8 ppm or reduced by 50% from the previous reading to receive payment for a day of abstinence.

Appendix Figure 1. CONSORT diagram.



[a]Participants were placed on the waiting list if the lab schedule was full, or if nearing final study randomization.
[b]Personal reasons include reasons not related to the study such as time commitment, loss of interest, moved out of the area.

[c]Withdrawn at Week 2 for elevated CO (99ppm).
[d]Withdrawn at Week 4 following a visit to the emergency room for excessive alcohol use.
[e]Withdrawn at Week 1 following a recurrence of breast cancer.
[f]Withdrawn at Week 1 following hospitalization after unrelated accident.
[g]Participant did not meet eligibility criteria due to excessive binge drinking and should not have been randomized, was withdrawn at Week 2 by principal investigator when mistake was discovered.

NNC, normal nicotine content; NRT, nicotine-replacement therapy; VLNC, very low nicotine content; IVR, interactive voice response.

Appendix Table 1. Means and SDs for Respiratory Health, Blood Pressure, Heart Rate

Variable	Baseline Mean (SD)	Week 1 Mean (SD)	Week 2 Mean (SD)	Week 3 Mean (SD)	Week 4 Mean (SD)	Week 5 Mean (SD)	Week 6 Mean (SD)
Average respiratory health score[a]							
NNC only	2.69 (1.58)	2.26 (1.26)	2.23 (1.23)	2.27 (1.21)	2.38 (1.62)	2.30 (1.43)	2.20 (1.41)
NNC + NRT	3.09 (1.68)	2.82 (1.47)	2.74 (1.44)	2.55 (1.35)	2.54 (1.42)	2.31 (1.19)	2.21 (1.02)
VLNC only	2.98 (1.72)	3.20 (1.86)	3.06 (1.69)	2.77 (1.40)	2.86 (1.56)	2.64 (1.38)	2.61 (1.51)
VLNC + NRT	3.17 (1.73)	3.1 (1.84)	3.04 (1.79)	2.87 (1.71)	2.90 (1.97)	2.73 (1.70)	2.60 (1.51)
Cough item							
NNC only	2.80 (1.83)	2.30 (1.41)	2.41 (1.61)	2.33 (1.51)	2.62 (1.93)	2.66 (1.97)	2.39 (1.77)
NNC + NRT	3.19 (1.93)	2.88 (1.66)	2.80 (1.66)	2.63 (1.61)	2.42 (1.51)	2.34 (1.47)	2.19 (1.41)
VLNC only	3.07 (2.16)	3.45 (2.22)	3.08 (2.07)	2.88 (1.87)	3.02 (1.85)	2.70 (1.65)	2.83 (1.88)
VLNC + NRT	3.23 (2.09)	3.15 (2.23)	3.10 (2.34)	2.90 (1.99)	2.90 (2.25)	2.85 (2.11)	2.67 (1.91)
Phlegm production item							
NNC only	2.85 (1.92)	2.30 (1.48)	2.41 (1.65)	2.62 (1.68)	2.52 (1.97)	2.31 (1.76)	2.23 (1.74)
NNC + NRT	3.27 (2.17)	2.95 (1.81)	2.75 (1.72)	2.66 (1.72)	2.68 (1.73)	2.58 (1.71)	2.54 (1.52)
VLNC only	3.15 (2.12)	3.27 (2.23)	3.03 (2.17)	2.80 (1.89)	3.03 (2.12)	2.70 (1.95)	2.72 (2.08)
VLNC + NRT	3.72 (2.16)	3.20 (2.09)	3.35 (2.18)	3.10 (2.21)	2.95 (2.13)	2.85 (1.99)	2.67 (1.77)
Shortness of breath item							
NNC only	2.97 (1.87)	2.51 (1.53)	2.36 (1.43)	2.31 (1.54)	2.33 (1.67)	2.20 (1.46)	2.05 (1.45)
NNC + NRT	3.46 (2.10)	3.15 (1.96)	3.08 (1.93)	2.95 (1.87)	2.86 (1.82)	2.49 (1.66)	2.46 (1.56)
VLNC only	3.48 (2.27)	3.38 (2.31)	3.27 (2.10)	3.07 (2.05)	2.95 (1.95)	3.08 (2.14)	2.78 (1.78)
VLNC + NRT	3.33 (2.11)	3.23 (2.10)	3.15 (2.03)	3.03 (2.00)	3.05 (2.23)	2.95 (2.05)	2.83 (2.09)
Irritation in the throat and lungs item							
NNC only	2.13 (1.54)	1.93 (1.55)	1.75 (1.12)	1.84 (1.24)	2.03 (1.73)	2.02 (1.51)	2.11 (1.73)
NNC + NRT	2.46 (1.71)	2.29 (1.68)	2.32 (1.63)	1.95 (1.42)	2.20 (1.72)	1.85 (1.36)	1.64 (0.96)
VLNC only	2.23 (1.73)	2.72 (2.24)	2.85 (2.25)	2.35 (1.67)	2.43 (1.95)	2.07 (1.49)	2.10 (1.56)
VLNC + NRT	2.40 (1.87)	2.80 (2.06)	2.55 (1.97)	2.43 (1.85)	2.68 (2.28)	2.25 (1.73)	2.22 (1.58)
Systolic blood pressure							
NNC only	126.70 (13.66)	126.49 (15.30)	125.62 (13.38)	124.98 (13.49)	128.33 (13.13)	128.62 (12.54)	127.34 (15.57)
NNC + NRT	127.02 (14.83)	128.53 (13.53)	128.92 (14.52)	128.95 (14.09)	130.47 (11.05)	129.81 (11.84)	129.05 (14.48)
VLNC only	125.23 (14.00)	125.43 (14.64)	125.12 (13.67)	125.90 (15.91)	123.52 (14.75)	123.67 (15.05)	123.83 (14.65)
VLNC + NRT	122.53 (15.47)	123.37 (15.56)	123.77 (13.30)	124.12 (13.95)	123.98 (14.83)	124.50 (13.17)	124.05 (11.97)
Diastolic blood pressure							
NNC only	79.82 (10.48)	80.33 (11.71)	80.59 (11.17)	80.18 (10.94)	81.90 (10.97)	81.36 (10.70)	80.97 (10.88)
NNC + NRT	80.34 (11.52)	82.15 (11.07)	81.63 (10.83)	80.39 (11.48)	81.81 (10.01)	81.86 (11.31)	81.42 (10.89)
VLNC only	76.65 (11.00)	77.30 (11.31)	77.28 (11.32)	78.30 (12.25)	77.50 (11.74)	76.73 (11.65)	77.20 (11.86)
VLNC + NRT	75.65 (11.10)	76.10 (10.86)	75.67 (10.76)	75.38 (9.84)	75.13 (9.61)	75.95 (11.21)	75.92 (10.51)
Heart rate							
NNC only	77.57 (10.50)	79.84 (11.86)	78.15 (12.87)	78.85 (12.52)	78.13 (12.07)	77.79 (11.06)	74.44 (11.34)

NNC + NRT	77.83 (13.71)	78.22 (12.28)	77.53 (13.01)	78.56 (13.38)	76.78 (12.07)	78.02 (13.10)	78.10 (12.00)
VLNC only	76.15 (11.81)	74.63 (12.66)	74.38 (12.88)	74.58 (12.66)	75.05 (11.84)	76.07 (12.36)	73.37 (11.89)
VLNC + NRT	73.55 (11.80)	74.30 (12.26)	74.53 (12.67)	74.65 (13.54)	73.67 (12.58)	73.33 (11.65)	74.60 (11.11)

[a]Average score on a Respiratory Health Questionnaire in which participants rated their cough, phlegm (mucous) production, shortness of breath, and irritation in the throat and lungs on a scale from none (1) to severe (10).

NNC, normal nicotine content; VLNC, very low nicotine content; NRT, nicotine replacement therapy.

Appendix Table 2. Statistical Results for Respiratory Health, Blood Pressure, Heart Rate

	VLNC		NRT		Interaction	
Linear mixed model[a]	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**
Average respiratory health score[b]	**0.41 (0.1, 0.72)**	**0.009**	0.02 (–0.29, 0.33)	0.908	–0.12 (–0.56, 0.33)	0.607
Cough item	**0.39 (0.03, 0.76)**	**0.036**	–0.13 (–0.49, 0.24)	0.506	–0.03 (–0.55, 0.49)	0.896
Phlegm production item	0.38 (–0.06, 0.82)	0.093	0.09 (–0.35, 0.53)	0.693	–0.27 (–0.89, 0.36)	0.399
Shortness of breath item	**0.49 (0.1, 0.89)**	**0.015**	0.25 (–0.15, 0.65)	0.221	–0.21 (–0.78, 0.35)	0.464
Irritation in the throat and lungs item[c]	–0.07 (–0.6, 0.46)	0.802	**–0.63 (–1.16, –0.1)**	**0.019**	0.67 (–0.08, 1.42)	0.081
Systolic blood pressure	–1.36 (–4.04, 1.31)	0.318	2.19 (–0.5, 4.87)	0.111	–1.06 (–4.87, 2.74)	0.585
Diastolic blood pressure	–1.36 (–3.63, 0.9)	0.238	0.31 (–1.95, 2.58)	0.788	–1.36 (–4.56, 1.85)	0.407
Heart rate	–2.33 (–5.03, 0.36)	0.090	–0.15 (–2.86, 2.55)	0.912	1.22 (–2.61, 5.05	0.533

Note: Boldface indicates statistical significance ($p<0.05$).

[a]Adjusted for baseline and menthol status.

[b]Average score on a Respiratory Health Questionnaire in which participants rated their cough, phlegm (mucous) production, shortness of breath, and irritation in the throat and lungs on a scale from none (1) to severe (10).

[c]Significant visit by treatment interaction, and visit included in model.

VLNC, very low nicotine content; NRT, nicotine replacement therapy; MD, mean difference.

Appendix Table 3. Patch Adherence by Week

Week	NRT on at least 50% of days[a]		NRT on at least 85% of days[a]	
	NNC + NRT (*n*=59) n (%)	VLNC + NRT (*n*=60) n (%)	NNC + NRT (*n*=59) n (%)	VLNC + NRT (*n*=60) n (%)
Week 1	56 (94.9)	51 (85.0)	47 (79.7)	42 (70)
Week 2	55 (93.2)	46 (76.7)	50 (84.7)	41 (68.3)
Week 3	53 (89.8)	43 (71.7)	48 (81.4)	41 (68.3)
Week 4	51 (86.4)	42 (70.0)	47 (79.7)	39 (65)
Week 5	50 (84.7)	43 (71.7)	49 (83.1)	37 (61.7)
Week 6	44 (74.6)	43 (71.7)	42 (71.2)	41 (68.3)

[a]Missing data included as not meeting criteria for patch compliance.

NNC, normal nicotine content; VLNC, very low nicotine content; NRT, nicotine replacement therapy.

Appendix Table 4. Means and SDs for Total Cigarettes per Day, Study Cigarettes per Day, Carbon Monoxide, and Total Puff Volume

Variable	Baseline Mean (SD)	Week 1 Mean (SD)	Week 2 Mean (SD)	Week 3 Mean (SD)	Week 4 Mean (SD)	Week 5 Mean (SD)	Week 6 Mean (SD)
Total cigarettes per day							
NNC only	17.94 (8.15)	20.59 (10.23)	21.40 (11.20)	21.82 (11.55)	22.27 (11.72)	21.92 (11.60)	21.76 (11.47)
NNC + NRT	19.65 (10.06)	21.80 (13.18)	20.74 (12.58)	20.80 (12.98)	20.50 (13.08)	21.33 (13.84)	21.00 (12.78)
VLNC only	18.68 (9.32)	22.72 (13.49)	20.91 (13.06)	19.85 (13.03)	18.84 (12.48)	18.63 (11.49)	18.03 (11.50)
VLNC + NRT	21.50 (13.13)	23.58 (17.63)	22.01 (17.43)	21.17 (17.46)	21.33 (18.54)	20.69 (17.74)	20.43 (18.69)
Study cigarettes per day							
NNC only	17.94 (8.15)	19.84 (10.37)	20.73 (11.76)	20.79 (11.74)	21.36 (11.76)	20.79 (11.47)	20.78 (11.46)
NNC + NRT	19.65 (10.06)	20.86 (13.33)	19.93 (12.61)	19.72 (12.89)	19.62 (13.23)	20.44 (13.28)	20.16 (12.70)
VLNC only	18.68 (9.32)	20.10 (14.14)	18.09 (13.63)	17.26 (13.48)	15.92 (13.08)	15.55 (12.04)	15.27 (12.07)
VLNC + NRT	21.50 (13.13)	21.70 (18.16)	20.04 (18.44)	18.80 (18.67)	18.42 (19.78)	18.30 (18.82)	18.12 (19.68)
Carbon monoxide (ppm)							
NNC only	23.9 (12.0)	23.7 (11.7)	24.3 (14.9)	25.3 (15.8)	24.4 (15.0)	23.7 (15.1)	23.6 (15.8)
NNC + NRT	23.2 (10.6)	24.3 (12.2)	22.8 (11.7)	21.3 (11.7)	21.3 (11.0)	21.7 (11.4)	23.5 (12.9)
VLNC only	25.4 (13.2)	25.4 (14.5)	25.3 (11.8)	25.7 (15.4)	25.7 (16.0)	24.3 (13.3)	23.7 (15.3)
VLNC + NRT	25.4 (11.9)	25.4 (16.9)	25.1 (13.8)	23.9 (14.7)	23.3 (13.3)	21.2 (11.8)	21.8 (12.9)
Total puff volume (ml)[a]							
NNC only	645.06 (205.35)		651.15 (222.04)				669.42 (221.77)
NNC + NRT	828.46 (472.12)		671.81 (264.77)				682.65 (232.42)
VLNC only	755.72 (298.77)		652.62 (299.50)				628.06 (310.94)
VLNC + NRT	730.52 (296.66)		564.65 (259.39)				590.36 (256.36)

[a]Total puff volume collected at Baseline, Week 2, and Week 6.

NNC, normal nicotine content; VLNC, very low nicotine content; NRT, nicotine replacement therapy; ppm, parts per million; ml, milliliter.

Appendix Table 5. Statistical Results for Cigarettes per Day, Expired Carbon Monoxide, Total Puff Volume During Puff Topography Assessment

	VLNC		NRT		Interaction	
Linear mixed model[a]	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**
Total cigarettes per day[b]	**–4.58 (–7.18, –1.97)**	**0.001**	**–2.74 (–5.36, –0.012)**	**0.040**	1.88 (–1.82, 5.58)	0.319
Study cigarettes per day[b]	**–6.35 (–9.27, –3.44)**	**<0.001**	–2.58 (–5.51, 0.36)	0.085	2.18 (–1.96, 6.33)	0.302
Carbon monoxide (ppm)[b]	–1.12 (–4.6, 2.36)	0.528	0.5 (–2.99, 4)	0.777	–2.48 (–7.42, 2.47)	0.326
Total puff volume (ml)	–60.44 (–139.24, 18.35)	0.133	–38 (–119.68, 43.67)	0.362	–16.81 (129.48, 95.86)	0.770

Notes: Boldface indicates statistical significance ($p<0.05$).

[a]Adjusted for baseline and menthol status.

[b]Significant visit by treatment interaction, and visit included in model.

VLNC, very low nicotine content; NRT, nicotine replacement therapy; MD, mean difference; ppm, parts per million; ml, milliliter.

Appendix Table 6. Statistical Results for Test of Menthol by Treatment Interaction

	VLNC		NRT		Interaction	
Linear regression[a]	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**
Menthol	–3.22 (–7.23, 0.79)	0.118	–1.30 (–5.30, 2.70)	0.525	0.79 (–4.87, 6.46)	0.784
Non-menthol	**–5.91 (–10.10, –1.72)**	**0.007**	–3.84 (–8.09, 0.42)	0.080	2.72 (–3.27, 8.70)	0.375

Notes: *p*-value for interaction=0.762. Boldface indicated statistical significance ($p<0.05$).
[a]Adjusted for baseline cigarettes per day.

VLNC, very low nicotine content; NRT, nicotine replacement therapy, MD, mean difference.

Appendix Table 7. Summary of Adherence With Study Cigarettes at Week 6

Variable	NNC only (*n*=61) n (%)	NNC + NRT (*n*=59) n (%)	VLNC only (*n*=60) n (%)	VLNC + NRT (*n*=60) n (%)
Total anatabine <0.014[a]	5 (8.2)	8 (13.6)	22 (36.7)	30 (50.0)
Self-reported 0 non-study cigarettes (100% adherence)[a]	49 (80.3)	42 (71.2)	18 (30.0)	24 (40.0)
Total anatabine <0.014 and self-reported 0 non-study cigarettes[a]	5 (8.2)	6 (10.2)	15 (25.0)	21 (35.0)
90% adherence with study cigarettes[a]	52 (85.2)	47 (79.7)	26 (43.3)	36 (60.0)
75% adherence with study cigarettes[a]	53 (86.9)	50 (84.7)	36 (60.0)	40 (66.7)
50% adherence with study cigarettes[a]	53 (86.9)	51 (86.4)	41 (68.3)	45 (75.0)

[a]Missing data included as not meeting criteria for adherence.

NNC, normal nicotine content; NRT, nicotine replacement therapy; VLNC, very low nicotine content.

Appendix Table 8. Statistical Results for Self-Reported Cigarette Adherence in Week 6

Self-reported adherence	VLNC		NRT		Interaction	
	Coefficient (95% CI)	***p*-value**	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**
Logistic regression[a]	**–2.36 (–3.23, –1.5)**	**<0.001**	–0.52 (–1.38, 0.34)	0.238	0.99 (–0.16, 2.15)	0.093
	NNC + NRT		**VLNC-only**		**VLNC+NRT**	
OR relative to NNC-only group[a,b]	0.6 (0.25, 1.41)	0.238	**0.09 (0.04, 0.22)**	**<0.001**	**0.15 (0.07, 0.35)**	**<0.001**

Notes: Boldface indicates statistical significance ($p<0.05$).
[a]Adjusted for menthol status.
[b]OR (95% CI).

NNC, normal nicotine content; NRT, nicotine replacement therapy; VLNC, very low nicotine content.

Appendix Table 9. Causal Inference Results

	VLNC		Interaction	
Causal inference model[a]	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**
Total CPD	**–7.02 (–12.03, –2.52)**	**0.004**	1.8 (–4.03, 7.99)	0.566
FTND	**–0.79 (–1.45, –0.08)**	**0.028**	–0.24 (–1.27, 0.85)	0.634
WISDM	–2.43 (–7.44, 2.48)	0.366	4.5 (–1.49, 10.64)	0.152
QSU-F1	**–5.15 (–9.58, –0.62)**	**0.030**	4.91 (–1.65, 11.08)	0.144
QSU-F2	–2.34 (–5.28, 0.62)	0.112	1.47 (–2.73, 5.68)	0.478
MNWS	1.44 (–0.6, 3.72)	0.204	1.55 (–1.45, 4.56)	0.366
CO	**–9.27 (–17.5, –1.98)**	**0.012**	2.24 (–7.02, 12.53)	0.658
Days abstinent	0.98 (–0.32, 2.22)	0.118	0.62 (–1.22, 2.34)	0.522
Time to first lapse	0.74 (–0.38, 1.92)	0.184	0.72 (–0.94, 2.3)	0.422

Notes: Boldface indicates statistical significance ($p<0.05$).
[a]NRT effects are unchanged from intent to treat analysis

VLNC, very low nicotine content; MD, mean difference, FTND; CPD, cigarettes per day; FTND, Fagerstrom Test for Nicotine Dependence; WISDM, Wisconsin Inventory on Smoking Dependence Motives; QSU, Questionnaire of Smoking Urges; MNWS, Minnesota Nicotine Withdrawal Scale; CO, carbon monoxide.

Appendix Table 10. Geometric Means and IQR for Nicotine Exposure

	Baseline	Week 2	Week 6
Total nicotine equivalents (TNEs)[a]	**GM (IQR)**	**GM (IQR)**	**GM (IQR)**
NNC only	63.47 (49.25)	56.24 (53.2)	57.20 (64.80)
NNC + NRT	54.67 (46.35)	77.32 (86.85)	76.02 (95.25)
VLNC only	58.33 (55.40)	15.57 (60.98)	15.04 (76.58)
VLNC + NRT	71.18 (85.08)	48.81 (55.15)	44.25 (69.38)

[a]First void urine collected at Baseline, Week 2, and Week 6 and analyzed for total nicotine equivalents.

GM, geometric mean; NNC, normal nicotine content; NRT, nicotine replacement therapy; VLNC, very low nicotine content.

Appendix Table 11. Statistical Results for Nicotine Exposure

	VLNC		NRT		Interaction	
Total nicotine equivalents (TNEs)	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**
Linear mixed model[a]	**–1.25 (–1.64, –0.85)**	**<0.001**	0.38 (–0.02, 0.78)	0.062	**0.62 (0.05, 1.18)**	**0.034**
	NNC + NRT		**VLNC-only**		**VLNC+NRT**	
Ratio of geometric means relative to NNC-only at Week 6[a]	1.53 (0.99, 2.37)	0.054	**0.24 (0.15, 0.36)**	**<0.001**	0.74 (0.48, 1.14)	0.167

Notes: Boldface indicates statistical significance ($p<0.05$).
[a]Adjusted for baseline and menthol status.

VLNC, very low nicotine content; NRT, nicotine replacement therapy; MD, mean difference; NNC, normal nicotine content.

Appendix Table 12. Means and SDs for Dependence, Craving, and Withdrawal

Variable	Baseline Mean (SD)	Week 1 Mean (SD)	Week 2 Mean (SD)	Week 3 Mean (SD)	Week 4 Mean (SD)	Week 5 Mean (SD)	Week 6 Mean (SD)
FTND[a]							
NNC only	5.5 (2.1)		5.8 (2.2)				5.7 (2.2)
NNC + NRT	5.8 (2.1)		5.8 (2.3)				5.7 (2.4)
VLNC only	5.5 (1.9)		5.6 (2.0)				5.2 (2.3)
VLNC + NRT	5.9 (2.1)		5.9 (2.3)				5.3 (2.4)
WISDM[b]							
NNC only	39.8 (11.7)						37.3 (12.9)
NNC + NRT	45.3 (13.6)						40.9 (14.0)
VLNC only	40.5 (14.2)						36.4 (16.0)
VLNC + NRT	43.9 (14.8)						41.2 (15.2)
QSU							
NNC only	31.9 (16.5)	25.8 (13.8)	26.1 (15.2)	26.7 (15.1)	25.0 (14.2)	24.8 (14.9)	26.1 (15.3)
NNC + NRT	34.7 (15.5)	24.8 (16.7)	27.2 (17.0)	25.5 (16.9)	25.8 (16.7)	24.8 (16.2)	24.4 (14.3)
VLNC only	32.4 (16.7)	26.0 (17.1)	23.8 (16.2)	23.6 (16.2)	22.9 (16.1)	23.0 (15.5)	20.2 (15.0)
VLNC + NRT	35.5 (16.3)	25.8 (14.4)	25.6 (16.0)	24.0 (14.6)	24.1 (15.2)	23.4 (15.5)	22.4 (15.1)
QSU-Factor 1							
NNC only	20.3 (10.0)	16.7 (9.3)	16.3 (9.9)	16.6 (9.4)	15.7 (9.1)	15.4 (9.0)	15.9 (9.4)
NNC + NRT	21.9 (9.5)	15.0 (9.9)	16.5 (9.9)	15.1 (9.7)	15.5 (10.0)	15.0 (9.7)	14.6 (8.9)
VLNC only	20.9 (10.1)	16.1 (10.9)	14.2 (9.7)	14.4 (10.4)	14.0 (10.2)	14.1 (9.9)	12.2 (9.4)
VLNC + NRT	21.9 (8.9)	15.7 (9.4)	15.7 (10.2)	14.7 (9.5)	14.6 (9.9)	14.1 (10.1)	13.6 (9.9)
QSU-Factor 2							
NNC only	11.6 (7.7)	9.1 (5.6)	9.8 (6.5)	10.1 (6.7)	9.3 (6.2)	9.5 (6.5)	10.2 (6.6)
NNC + NRT	12.9 (7.4)	9.8 (7.5)	10.7 (7.9)	10.4 (7.8)	10.4 (7.7)	9.8 (7.3)	9.8 (6.4)
VLNC only	11.5 (7.5)	9.9 (7.1)	9.6 (7.2)	9.2 (6.8)	8.9 (6.8)	8.9 (6.3)	8.1 (6.2)
VLNC + NRT	13.6 (8.7)	10.0 (6.2)	9.9 (6.5)	9.4 (6.0)	9.5 (6.2)	9.3 (6.3)	8.9 (6.0)
MNWS							
NNC only	6.7 (4.8)	7.4 (5.3)	8.2 (6.0)	7.7 (5.6)	7.8 (6.8)	7.3 (6.4)	7.2 (5.8)
NNC + NRT	7.0 (4.6)	7.5 (4.6)	7.5 (4.7)	7.2 (4.7)	7.4 (5.0)	6.8 (5.0)	6.7 (4.9)
VLNC only	6.4 (3.9)	8.5 (6.0)	8.4 (5.5)	8.1 (5.6)	7.8 (6.0)	7.8 (6.5)	7.8 (6.1)
NNC only	7.4 (5.1)	10.2 (6.2)	9.7 (6.0)	8.5 (6.0)	9.2 (6.1)	9.3 (6.9)	9.2 (6.0)

[a]FTND collected at Baseline, Week 2, and Week 6.
[b]WISDM collected at Baseline and Week 6.

NNC, normal nicotine content; NRT, nicotine replacement therapy; VLNC, very low nicotine content; FTND, Fagerstrom Test for Nicotine Dependence; WISDM, Wisconsin Inventory on Smoking Dependence Motives; QSU, Questionnaire of Smoking Urges; MNWS, Minnesota Nicotine Withdrawal Scale.

Appendix Table 13. Statistical Results for Dependence, Craving, and Withdrawal

	VLNC		NRT		Interaction	
Linear mixed model[a]	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**	**MD (95% CI)**	***p*-value**
FTND	–0.33 (–0.8, 0.13)	0.163	–0.23 (–0.7, 0.24)	0.335	0.07 (–0.59, 0.73)	0.835
WISDM[b]	–1.45 (–4.59, 1.68)	0.365	–1.02 (–4.2, 2.17)	0.532	3.01 (–1.43, 7.46)	0.186
QSU	–2.74 (–6.66, 1.18)	0.171	–1.89 (–5.84, 2.05)	0.347	1.12 (–4.44, 6.69)	0.693
QSU-F1	–2.27 (–4.8, 0.26)	0.079	–1.66 (–4.21, 0.88)	0.201	1.7 (–1.89, 5.29)	0.354
QSU-F2[c]	**–1.99 (–3.86, –0.13)**	**0.036**	–1.03 (–2.91, 0.84)	0.280	0.73 (–1.93, 3.38)	0.592
MNWS	0.76 (–0.52, 2.05)	0.245	–0.58 (–1.87, 0.71)	0.380	1.07 (–0.76, 2.9)	0.251

Notes: Boldface indicates statistical significance ($p<0.05$).
[a]Adjusted for baseline and menthol status.
[b]WISDM was only collected at baseline and Week 6, so linear regression was used, rather than linear mixed model.
[c]Significant visit by treatment interaction, and visit included in model.

VLNC, very low nicotine content; NRT, nicotine replacement therapy; MD, mean difference; FTND, Fagerstrom Test for Nicotine Dependence; WISDM, Wisconsin Inventory on Smoking Dependence Motives; QSU, Questionnaire of Smoking Urges; MNWS, Minnesota Nicotine Withdrawal Scale.

Appendix Table 14. Week 7 Abstinence Incentive Means and Medians

Variable	Overall	NNC-only	NNC+NRT	VLNC-only	VLNC + NRT
Time to lapse (days)					
Mean (SD)	2.90 (2.38)	3.07 (2.39)	2.75 (2.35)	2.29 (2.19)	3.44 (2.50)
Median (range)	1.5 (0.5, 6.5)	1.5 (0.5, 6.5)	1.5 (0.5, 6.5)	1.5 (0.5, 6.5)	1.5 (0.5, 6.5)
Days abstinent					
Mean (SD)	3.15 (2.79)	3.27 (2.73)	3.16 (2.78)	2.35 (2.71)	3.78 (2.85)
Median (range)	3.0 (0.0, 7.0)	2.0 (0.0, 7.0)	3.0 (0.0, 7.0)	1.0 (0.0, 7.0)	4.0 (0.0, 7.0)

NNC, normal nicotine content; NRT, nicotine replacement therapy; VLNC, very low nicotine content.

Appendix Table 15. Statistical Results for Week 7 Abstinence Week

Variable	VLNC		NRT		Interaction	
	Hazard ratio (95% CI)	***p*-value**	**Hazard ratio (95% CI)**	***p*-value**	**Hazard ratio (95% CI)**	***p*-value**
Cox regression[a]						
Time to first lapse	1.48 (0.96, 2.29)	0.07	1.21 (0.79, 1.86)	0.38	**0.48 (0.26, 0.91)**	**0.02**
	NNC + NRT		**VLNC-only**		**VLNC+NRT**	
Pairwise comparisons with NNC-only as reference[a]						
Time to first lapse	1.21 (0.79, 1.86)	0.38	1.48 (0.96, 2.29)	0.07	0.87 (0.55, 1.36)	0.54
	VLNC		**NRT**		**Interaction**	
Linear regression[a,b]						
Days abstinent	–0.92 (–2.00, 0.15)	0.09	–0.14 (–1.20, 0.92)	0.80	**1.57 (0.03, 3.10)**	**0.046**
	NNC + NRT		**VLNC-only**		**VLNC+NRT**	
Pairwise comparisons with NNC-only as reference[a,b]						
Days abstinent	–0.14 (–1.20, 0.92)	0.8	–0.92 (–2.00, 0.15)	0.09	0.50 (–0.57, 1.57)	0.35

Notes: Boldface indicates statistical significance ($p<0.05$).
[a]Adjusted for menthol status
[b]MD (95% CI)
VLNC, very low nicotine content; NRT, nicotine replacement therapy; NNC, normal nicotine content.

APPENDIX REFERENCES

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PROJECT 1, STUDY 2:

THE COMBINED IMPACT OF NICOTINE REPLACEMENT AND SPECTRUM CIGARETTES

STUDY PROTOCOL

Table of Contents

Abbreviations

- VLNC: Very low nicotine content
- RNC: Reduced nicotine content
- NNC: Normal nicotine content
- CPD: Cigarettes per day
- NRT: Nicotine replacement therapy
- CO: Carbon monoxide
- BAL: Breath alcohol levels
- BP: Blood pressure
- HR: Heart rate
- BPM: Beats per minute
- NMR: Nicotine metabolite ratio
- NNN: *N*'-nitrosonornicotine
- NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
- BDI: Beck's Depression Inventory
- FTND: Fagerström Test for Nicotine Dependence
- WISDM: Wisconsin Index of Smoking Dependence Motives
- CESD: Center for Epidemiological Studies Depression Scale
- TLFB: Timeline Follow Back
- MNWS: Minnesota Nicotine Withdrawal Scale
- PANAS: Positive and Negative Affect Scale
- QSU: Questionnaire of Smoking Urges
- CES: Cigarette Evaluation Scale
- PSS: Perceived Stress Scale
- IVR: Interactive Voice Response
- CENIC: Center for the Evaluation of Nicotine in Cigarettes

CENIC Project 1, Study 2 Protocol

Objective

Project 1, Study 2 will evaluate the impact of very low nicotine content cigarettes with and without transdermal nicotine on cigarettes smoked per day, nicotine exposure, discomfort/dysfunction, other health-related behaviors, nicotine/tobacco dependence, biomarkers of tobacco exposure, intention to quit, compensatory smoking, other tobacco use, cigarette characteristics, cardiovascular function, perceived risk and cue reactivity. We will also consider differences between conditions in compliance with product use and the ability to abstain from smoking when provided a financial incentive for abstinence.

Background Information on Tobacco Regulation

Over 44 million people in the United States (CDC, 2000) and 1.2 billion worldwide smoke cigarettes (Shafey, 2009). With 440,000 deaths per year in the US and 6 million per year world-wide with speculations of 7 million deaths per year if current trends in smoking continue through 2020 (Shafey, 2009), it is critical to have strong tobacco control policies in place to minimize the casualties from tobacco use.

According to Orleans and Slade (1993) and Giovino (2002), there are four main targets for tobacco control: the Agent, the Vector, the Host and the Environment. The majority of recent tobacco control efforts have been aimed at the Host (tobacco prevention and cessation programs), the Environment (policies such as smoking bans, increased taxes, anti-smoking media campaigns, advertisement bans, pictorial warning labels) and the Vector (tobacco law suits). Relatively little attention has been focused on the Agent (the tobacco product). Altering tobacco products in ways to reduce mortality and morbidity that complement current tobacco control measures may be an important next step in our tobacco control efforts.

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) passed in 2009 provides the FDA with the authority to regulate tobacco products. One of the provisions in this legislative act empowers the FDA to reduce harmful constituents in tobacco products, including nicotine as long as the nicotine levels are not reduced to zero. Such a measure has the potential to reduce the chance of individuals experimenting with smoking from becoming dependent and enable current smokers to quit when they are motivated to do so. Although the proposal to reduce nicotine in cigarettes has been met with skepticism by some because of concerns over compensatory smoking behavior (Jarvis & Bates, 1999) and the emergence of a black market (Shatenstein, 1999), this policy measure was considered to be technically feasible by the American Medical Association and the British Medical Association (Henningfield et al., 1998) and by tobacco control researchers, policymakers and governmental officials who were convened in a meeting on nicotine regulation (Hatsukamiet al., 2010).

Effects of Very Low Nicotine Content Cigarettes

Studies of very low nicotine content cigarettes (VLNC; e.g., <0.1 mg nicotine yield) cigarettes suggest that, acutely, they produce many effects in smokers that are qualitatively similar to normal nicotine content (NNC; e.g., 0.8 mg yield) cigarettes, but with somewhat reduced efficacy. VLNC cigarettes reinforce behavior (Shahan et al., 1999; Shahan et al., 2001), maintaining similar rates of self-administration as NNC cigarettes despite the fact that participants prefer NNC cigarettes when given a choice (Shahan et al., 1999). Compared to not smoking, VLNC cigarettes increase ratings of satisfaction and liking (Donny et al., 2007; Donny & Jones, 2009; Rose et al., 2000), although the magnitude of these effects is typically reduced compared to those produced by NNC cigarettes (Butschky et al., 1995; Gross et al., 1997; Robinson et al., 2000). VLNC cigarettes also reduce withdrawal and craving (Pickworth et al., 1999), although some symptoms (e.g., restlessness, impatience) may be more effectively alleviated by NNC cigarettes (Buchhalter et al., 2005). Much less is known about the effects of VLNC cigarettes over an extended period

of use. When only VLNC cigarettes were available in an inpatient setting, the number of cigarettes smoked and the motivation to smoke during periods of abstinence decreased over time (Donny et al., 2007). Longer, outpatient studies have found that smoking rates remained unchanged for a week after switching to VLNC cigarettes (Benowitz et al., 2007; Benowitz et al., 2009; Donny & Jones, 2009), but declined significantly over a period of 3-6 weeks (Hatsukami et al., 2010). During this time, participants also reported minimal withdrawal symptoms and a reduction in nicotine dependence as measured by the FTND (Hatsukami et al., 2010). These data suggest that the reinforcing effects of cigarettes may decline with extended use of VLNC cigarettes, but that the process is on the order of weeks rather than days. Finally, it is important to note that there is little evidence to suggest that prolonged use of VLNC cigarettes will result in a compensatory increase in smoking. Data available to date indicate that smoking is first maintained at a similar rate compared to preferred brand and then decreases over time (Donny & Jones, 2009; Hatsukami et al., 2010). Furthermore, participants tend to reduce the volume of smoke inhaled and demonstrate a decrease in expired CO (Donny & Jones, 2009; Hatsukami et al., 2010). These findings are in contrast to reports indicating an acute compensatory increase in total puff volume in participants smoking VLNC cigarettes (Strasser et al., 2007). Hence, VLNC cigarettes may produce a short-lived compensatory increase in smoking, but this effect likely dissipates quickly and is replaced by a decrease in smoke intake. Nevertheless, the study proposed below will assess puff topography and markers of exposure to continue to address concerns about possible compensatory use of VLNC cigarettes.

Very Low Nicotine Content Cigarettes and Transdermal Nicotine

Reducing nicotine content has the potential to reduce cigarette reinforcement and dependence, which in turn may result in less consumption per individual smoker and a greater likelihood of quitting. This move could save millions of lives; however, critical questions must be addressed before this policy can be considered. One such question is whether adjunct nicotine replacement facilitates the transition to VLNC cigarettes. Early studies of relatively short duration (≤2 weeks) suggested that concurrent transdermal nicotine decreases use of VLNC cigarettes and tends to reduce drop-out rate (Becker et al. 2008;Donny and Jones 2009; Hatsukami et al. 2013). A more recent, six week study of VLNC cigarettes and transdermal nicotine in treatment-seeking smokers (Hatsukami et al., 2013), found that the combination group (VLNC cigarettes and nicotine patch) smoked significantly fewer study cigarettes, had less non-compliance (i.e. smoking usual brand) and lower carbon monoxide levels when compared to subjects who received either just the nicotine patch or just the VLNC cigarettes.

In the present study, we propose to evaluate the effects of nicotine replacement and/or VLNC cigarettes in non-treatment seeking smokers over a 7 week period. Importantly, the combination of nicotine replacement and smoking poses little additional risk compared to either alone. Indeed, after reviewing decades of scientific literature, the FDA has recommended companies remove warning labels on nicotine replacement products that indicate smoking while using the product poses an increased health risk to consumers (FDA, 2013).

Overall Study Design

Screening/Baseline	Randomization	Week 1 Visit	Week 2 Visit	Week 3 visit	Week 4 Visit	Week 5 Visit	Week 6 Visit	Abstinence Day 1	Abstinence Day 2	Abstinence Day 3	Abstinence Day 4	Abstinence Day 5	Abstinence Day 6	Abstinence Day 7	30 Day Follow Up
92	**00**	**01**	**02**	**03**	**04**	**05**	**06**	**71**	72	73	74	75	76	**77**	30
Smoking Phase								Non-Smoking Phase							
Usual Brand	Spectrum Brand														
Lab								Home						**Lab**	Call

Screening/Baseline Visit

Recruitment

Participants will be recruited through flyers, direct mailings, television, radio, newspaper, bus, online via our recruitment website, the CTSI Registry, and Craigslist advertisements that read "Smokers who want to try new cigarettes that may or may not lead to reduced smoking are wanted for a research study. This study is not intended as a treatment for smoking. Participants will be paid for participation." Those who call into the laboratory will be read a script briefly explaining the study. After verbal informed consent is received, the participants will be asked questions over the phone to determine initial eligibility. If eligible and interested, they will be scheduled for an informational session during which they will be provided with a copy of the consent document and shown a PowerPoint presentation that outlines the procedures, benefits/risks, compensation and the participants' rights. They will also be able to ask questions about the study. If they are still interested in the study, then they will be scheduled for an in-person screening interview. Potential participants will be instructed to bring a pack of their usual brand cigarettes as well as all prescription medications they are currently taking to the screening visit.

Potential participants will be instructed to bring a valid, state issued photo ID to the screening visit. Acceptable forms of identification include a Driver's License, State Photo ID Card, State Voter ID Card, Passport, or Military ID. If the potential participant does not have a valid, state issued photo ID, the interviewer can provide him/her with information on obtaining one.

A participant must complete his/her in-person screening session within 30 days of completing the telephone recruitment questionnaire. If the participant is not able to attend the in-person screening visit in that timeframe, he/she will need to complete the telephone recruitment questionnaire again but will maintain the same REDCap ID number.

Informed Consent Process

Before beginning the informed consent process, potential participants will need to produce valid, state issued photo identification. The interviewer will confirm the age and identity of the participant. If the participant is not age 18 or older, he/she will be dismissed without payment. During the in-person

screening session, study information will be presented and written informed consent will be required to participate in the screening. In order to ensure adequate informed consent, participants will be asked to read the first several lines aloud (to determine literacy) and will then be given ample time to read the consent document. If the interviewer determines that the participant is not literate, he/she will dismiss the person from the study. The interviewer will review the PowerPoint presentation if necessary. The participant will be instructed to read several open-ended questions aloud and discuss the answers with the researcher. Only after the participant and the researcher are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and his/her rights as a research participant will the consent form be signed and the participant undergo screening procedures.

Screening Procedures

The following physiological measures will be collected, recorded on paper, and entered into REDCap by the interviewer at the end of the visit:

1) Breath alcohol levels (BAL) will be measured using an Alcosensor monitor. Participants with levels over 0.01 g/l will not be eligible to participate.
2) Weight and height**,** will be measured to determine the participant's Body Mass Index. Weight will be measured in kilograms and height will be measured in centimeters.
3) Expired breath carbon monoxide (CO) levels will be assessed using a Smokerlyzer Micro+ CO meter (Bedfont Instruments), a reliable and valid measure of recent smoking. These devices will be used for in-lab assessments only. A minimum of two breath samples will be completed for each CO reading and the average of the two will be used as the final CO. However, if the average of the two readings differs by more than 2 ppm, a third sample will be needed. The final CO will now be the average of all three breath samples.
    a. NicAlert Strips will be used to assess urinary cotinine levels if a participant's carbon monoxide reading is less than or equal to 9 ppm.
4) A urine toxicological screen will be performed to assess the presence of illicit drugs including marijuana, cocaine, opiates, benzodiazepines, barbiturates, amphetamines, methadone, methamphetamines, and PCP.
5) Pregnancy Tests (HCG detection) will be performed for female participants with childbearing potential. We will also ask the date of last menstrual period and length of cycle.
6) Blood pressure and heart rate will be measured using a CritiCare monitor to help the licensed medical professional determine final participant eligibility.

The following screening questionnaires will be participant-administered via paper and then will be entered into the study databases by the interviewer at the end of the visit:

1) Identifying Information Form will include the participant's Subject Identifier, name, address (including the county of residence), email address, phone number, age, date of birth, and social security number.
    a. This form will be entered into the 'Identifying Information Access Database'.
        i. Identifying information will be kept in a locked file cabinet (source document) and in a password protected Access Database (electronic version) separate from all other study data.
2) Brief Medical History Questionnaire to assess current diagnoses, symptoms and past health problems.
    a. Sections of the questionnaire will be entered into REDCap.

b. The medications section will be transferred to the 'Concomitant Medications' form in REDCap.

3) Prime MD, a brief questionnaire developed for evaluation of mental disorders by primary care physicians (Spitzer et al., 1999).
    a. This questionnaire will be entered into REDCap
4) Beck Depression Inventory (BDI; Beck, Ward, & Mendelson, 1961), if applicable, to assess depression in participants who endorse suicidal ideation or Major Depressive Disorder on the Prime MD.
    a. This questionnaire will be a **source document only**.

The following screening assessments will be administered as an interview and entered into REDCap by the interviewer:

1) Medical History Follow-Up Questionnaire, if applicable, to further assess current diagnoses, symptoms and past health problems.
    a. This questionnaire will be a **source document only**.
2) The Mini International Neuropsychiatric Interview (MINI) suicide subscale (Sheehan et al., 1997) to evaluate suicide risk.
3) Tobacco Use History and Exposure Questionnaire, which measures variables such as smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking.
4) Drug Use Questionnaire (12 month and 1 month version)
5) Smoking Cessation Therapy Use Questionnaire to assess use of nicotine replacement therapy or smoking cessation medications to help participants quit smoking as well as any adverse reactions participants may have experienced while using nicotine replacement.

The following screening assessments will be administered via Qualtrics:

1) Demographic History Questionnaire, which will assess age, gender, ethnicity, race, education, income, marital status, and employment history.
2) Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977), which measures symptoms of depression
3) Alcohol Use Questionnaire (12 month and 1 month version)
4) Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991)
5) Smoking Stages of Change Algorithm as well as a contemplation ladder to assess intention to quit smoking (DiClemente et al., 1991; Beiner et al., 1991).

In the event that the Qualtrics website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Qualtrics when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

Suicidality/Mental Health Monitoring

Participants who make any response other than "not at all" on the suicidal ideation question of the Prime MD (Question 1i) or indicate suicidal ideation or attempt in the past month or a suicide attempt in the past 5 years on the MINI suicide subscale will not be eligible to participate in the study. If the participant has attempted suicide between 6-10 years ago, then the LMP will have to approve eligibility. To determine if a participant is in immediate danger, refer to the licensed on-site clinician for evaluation. In the event that no clinician is available, staff will ask the participant two questions to determine level of risk: "Are you feeling suicidal?" and "Do you have a plan to kill yourself today?" If the participant has a plan to kill

himself/herself, staff will put the participant in contact with the Re:Solve at 1-888-796-8226. If the participant refuses to talk to the hotline and leaves, the study staff will call 911. They will also contact the Study Coordinator and Site PI to inform them of the situation as soon as possible. If the participant does not have a plan to kill himself/herself, the study staff will recommend he/she speaks with the suicide hotline and inform him/her that he/she will not be eligible for the study. The participant will be paid $25 and provided with local mental health resources.

Additionally, any participant whose score on the Prime MD indicates Major Depressive Disorder will be administered the Beck Depression Inventory (BDI) on paper. The BDI will be submitted, along with the Prime MD, Brief Medical History Questionnaire, Brief Medical History Follow-up Questionnaire, and the MINI suicide subscale to the licensed medical professional for eligibility review. If he/she determines a participant with Major Depressive Disorder is eligible for study participation, the participant will complete the BDI on a weekly basis to monitor changes in his/her mood.

Inclusion Criteria:

1) Age 18+
2) Daily smokers who smoke an average of at least five cigarettes per day for the last year with no periods of continuous abstinence longer than 30 days.
3) Breath CO levels $\geq$ 10 ppm (if < 10 ppm, then NicAlert Strip = 6)
4) Fulfills need for participants in the required strata (menthol status)

Exclusion Criteria:

1) Intention to quit smoking in the next 30 days
2) Currently seeking treatment for smoking cessation
3) Currently using nicotine replacement therapies or other pharmacotherapies as cessation aid (intermittent use acceptable)
4) Significant prior adverse reaction to nicotine replacement as determined by the licensed medical professional.
5) A quit attempt in the past 30 days resulting in greater than 3 days of abstinence
6) Using other tobacco products more than 9 days in the past 30 days
7) Significant unstable medical conditions (any significant **change** in a serious medical condition occurring during the past 3 months including cardiovascular disease, COPD, and cancer, as determined by the licensed medical professional)
8) Significant unstable psychiatric conditions (any significant **change** in psychiatric symptoms during the past 3 months as determined by the licensed medical professional)
9) Schizophrenia and schizoaffective disorder
10) Positive toxicology screen for any of the following drugs: marijuana, cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, and PCP
    a. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone will not be excluded.
11) Breath alcohol level > 0.01
12) Binge drinking alcohol (more than 9 days in the past 30 days, 4/5 drinks in a 2 hour period (female/male))
13) Pregnant, trying to become pregnant or breastfeeding
14) Smoking 'roll your own cigarettes' exclusively
15) Currently taking any one of the following medications:
    a. Phenytoin [Brand Name: Dilantin]
    b. Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Epitol]

c. Oxcarbazepine [Brand Name: Trileptal]
d. Primidone [Brand Name: Mysoline]
e. Phenobarbital
f. Bendamustine [Brand Name: Treanda]
g. Clopidogrel [Brand Name: Plavix]
h. Clozapine [Brand Name: Clozaril, FazaClo]
i. Erlotinib [Brand Name: Tarceva]
j. Flecainide [Brand Name: Tambocor]
k. Fluvoxamine [Brand Name: Luvox]
l. Irinotecan [Brand Name: Camptosar]
m. Olanzapine [Brand Name: Zyprexa]
n. Ropinirole [Brand Name: Requip]
o. Tacrine [Brand Name: Cognex]
p. Theophylline [Brand Name: Theo Dur]
q. Estradiol

16) CO reading >80 ppm
17) Systolic BP greater than or equal to 160
    a. Participants failing for blood pressure will be allowed to re-screen once.
18) Diastolic BP greater than or equal to 100
    a. Participants failing for blood pressure will be allowed to re-screen once.
19) Systolic BP below 90
    a. Participants failing for blood pressure will be allowed to re-screen once.
20) Diastolic BP below 50
    a. Participants failing for blood pressure will be allowed to re-screen once.
21) Heart rate greater than or equal to 105 bpm
    a. Participants failing for heart rate will be allowed to re-screen once.
22) Heart rate lower than 45 bpm
    a. Participants failing for heart rate will be allowed to re-screen once.
23) Indicating any suicidal ideation in the past month or suicide attempts in the past 5 years (if within the past 6-10 years, LMP approval required).
24) Inability to independently read and comprehend the consent form and other written study materials and measures.
25) Having participated in a research study during the past three months in which the participant:
    a. Smoked a cigarette that was not his/her usual brand cigarette for more than one day
    b. Used any tobacco products beyond normal use for more than one day
    c. Used any nicotine replacement products or smoking cessation medications for more than one day
26) Having participated in Project 1, Study 1 (PRO11060292)
27) Having participated in Project 1, Study 1C (PRO14040384)
28) Household member enrolled in the study concurrently
29) Significant prior adverse reactions to adhesives or latex

Children under age 18 are excluded because they cannot legally buy cigarettes. Those with unstable medical or psychiatric conditions or a prior adverse reaction to nicotine replacement are excluded as these symptoms could affect a participant's ability to complete the study. Examples include but are not limited to the following: angina, stroke, heart attack which occurred since phone screening, blood clots in the

arms or legs for which the individual is undergoing active medical treatment, cancer requiring active chemotherapy or radiation therapy, severe shortness of breath caused by conditions such as uncontrolled asthma, COPD, or arrhythmia, active untreated infection such as pneumonia, active untreated endocrine disorder such as hyperthyroidism. We will exclude those currently seeking smoking treatment, those who have quit smoking for longer than 3 days in the past 30 days or are planning to quit in the next 30 days, as participation in this study may not lead to reductions in smoking. We will exclude pregnant and nursing women and anyone with current or recent alcohol or drug abuse problems as these factors could independently affect smoking behavior during the study. Individuals with baseline CO readings greater than 80 ppm, those with heart rate or blood pressure readings that are out of range and anyone who has attempted suicide in the past five years will be excluded from the study for safety concerns. Individuals who smoke 'roll your own' cigarettes exclusively will be excluded from the study because we will be unable to standardize their baseline smoking behavior. Participants that are currently prescribed one of the medications listed will be excluded because this medication could interfere with the biomarkers or possibly cause an adverse smoking-drug interaction if there are changes in smoking behavior. If an individual has recently participated in a smoking research study that changed his/her smoking behavior this person would be excluded because he/she would not have a stable smoking baseline. Because participants are required to complete portions of the protocol independently both in the lab and at home, they will need to be able to independently read and comprehend the study materials. Multiple participants within the same household may not enroll concurrently to avoid product exchanging. Because participants may be assigned to wear a nicotine patch, we are excluding anyone with significant prior adverse reactions to adhesives or latex.

Eligibility Determination

Research staff will determine initial eligibility after reviewing all eligibility criteria except for the medical/psychiatric history. If the participant is deemed eligible, he/she will continue the visit and complete additional baseline measures (listed below).

Final eligibility of the participant will be determined by a licensed medical professional after reviewing the Brief Medical History Questionnaire, Medical History Follow-Up Questionnaire and the MINI suicide subscale. If the participant's score on the Prime MD indicates a psychiatric disorder then the Prime MD will be submitted to the licensed medical professional for review as well. Additionally, if the participant's score on the Prime MD indicates Major Depressive Disorder, then the Prime MD along with the Beck Depression Inventory will be submitted for review. He/she will sign off on eligibility prior to the Randomization Visit, that the participant is medically stable to receive the study product(s). If the licensed medical professional determines the participant is not medically eligible to receive study product(s), then the research staff will contact the participant prior to the Randomization Visit. The licensed medical professional will not review the medical history forms of participants who are not eligible for other, non-medical reasons.

Once all the screening procedures have been completed, researchers will pay ineligible participants $25 for their time as long as they pass the drug and breath alcohol tests and meet the minimum requirements for carbon monoxide or NicAlert levels. Those participants who do not pass these tests or meet these requirements will be dismissed from the study without payment. If a participant does not pass the drug test but has a current, valid prescription that would explain the failed test, then he/she will not be automatically excluded and will still receive $25. Participants who meet the initial eligibility criteria, and complete additional baseline measures, will be paid $50.

Baseline Procedures for Eligible Participants ONLY

The following assessments will be administered using Qualtrics:

1) Wisconsin Index of Smoking Dependence Motives-Brief (WISDM; Piper et al., 2008), a measure of tobacco dependence
2) Perceived Health Risks Rating (Hatsukami et al., 2010), a measure of the perceived addictive potential and other health risks associated with cigarettes
3) Perceived Stress Scale - 4 item (PSS-4; Cohen, Kamarck, & Mermelstein, 1983), which measures the degree to which life situations are appraised as stressful
4) Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegan, 1988), which measures symptoms of positive and negative affect.
5) Respiratory Health Questionnaire, a measure of cough, shortness of breath and other respiratory symptoms
6) Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), a measure of nicotine withdrawal
7) Questionnaire of Smoking Urges-brief scale - Usual Cigarette (QSU; Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991), which measures the urge to smoke
8) Cigarette Evaluation Scale (CES; Westman, Levin, & Rose, 1992), which measures responses to cigarettes (e.g., reward, satisfaction)

Interactive Voice Response System:

Participants will also be trained to use the Interactive Voice Response (IVR) System, which will contact participants each day throughout the study and ask about their smoking behavior as well as withdrawal symptoms the week before and after randomization. Participants will be provided a study cell phone if they have unreliable telephone access, do not have enough monthly cell phone minutes or prefer not to use their own phone.

The IVR system is operated by InterVision Media, a media production company. To be enrolled in the IVR system, research staff will enter the participant's initials, telephone number, subject identifier, and visit dates into the IVR CENIC website. Identifying information (initials and telephone numbers) will not be extracted with the data by the bioinformatics group. Please refer to InterVision Media's privacy statement and HIPAA compliance form for additional information.

At the end of the Screening/Baseline Visit, the researcher will complete the End of Visit Evaluation Form, which will be entered into REDCap. This will allow the researcher to make note of any problems encountered during the visit, to track which computers were used for which tasks, and to assess the truthfulness of the participant in regards to self-report of tobacco use.

Potential risks of participation

1) Survey Questionnaires: The interview will include questions about medical history, drug and alcohol use, and questionnaires about mood. Answering these personal questions could make the participant feel uncomfortable.
2) Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results.
3) Drug Testing: A breach of confidentiality could occur and other people could learn of the participant's drug use.
4) Obtaining blood pressure: The blood pressure cuff may cause minimal discomfort. In obtaining blood pressure, researchers may find out the participant has abnormal blood pressure.
5) Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to significant medical problems including:

a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
b. Respiratory Diseases: Emphysema, bronchitis, tuberculosis and chronic airway obstruction
c. Cancers: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia
d. Diabetes
e. Immune function, rheumatoid arthritis
f. Other Health Risks Associated with Smoking: Including but not limited to infertility, ectopic pregnancy, lower bone density in postmenopausal women, hip fracture in women, male sexual dysfunction; age-related macular degeneration, blindness and cataracts
g. Death

6) Smoking study cigarettes: In addition to the above medical problems, participants may experience some minor adverse health effects such as headaches or experience withdrawal symptoms which are listed below. Due to the altered nicotine levels, there could be a change in their cigarette use including the manner in which they inhale the smoke or increase the number of cigarettes smoked per day. This increased rate of smoking may persist after completing the study. Smoking the study cigarettes does not provide any less risk than their usual brand cigarette and could pose increased health risks. Participants may also experience increases in levels of carbon monoxide, a gas from smoke. The study cigarettes are made from genetically modified tobacco plants. A full toxicological evaluation has not been conducted, thus the consequences of inhaling this genetically modified product is unknown.
7) Smoking Withdrawal: Participants may experience smoking withdrawal symptoms during this study. The symptoms can be uncomfortable but are typically of minimal risk. Smoking withdrawal symptoms include:
    a. Anger, irritability, frustration
    b. Anxiousness, nervousness
    c. Depressed mood or sadness
    d. Desire or craving to smoke
    e. Difficulty concentrating
    f. Increased appetite, hunger or weight gain
    g. Insomnia, problems sleeping or awakening at night
    h. Restlessness
    i. Impatience
    j. Constipation
    k. Dizziness
    l. Coughing
    m. Dreaming or nightmares
    n. Nausea
    o. Sore Throat
8) Returning to Regular Smoking: It is possible that if participants return to smoking their usual brand of cigarette at the end of the study they may experience mild and transient nausea, dizziness, and lightheadedness.
9) Risk to Fetus**:** Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, low birth weight, problems with the placenta, birth defects such as cleft palate, sudden infant death syndrome (SIDS), and early childhood behavioral problems.

10) Changes in blood pressure and/or heart rate: Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate.
11) Changes in mood, emotions and psychiatric symptoms: Smoking and nicotine can affect a person's mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine or cigarette consumption could adversely affect mood, emotions and the symptoms related to psychiatric conditions in some individuals.
12) Smoking and oral contraceptives in women: Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician. Smoking while using oral contraceptives can increase the risk of having a cardiovascular event such as a heart attack or stroke. Additionally, there is a potential risk of thrombosis associated with hormonal therapy (including contraceptives) and smoking.
13) Smoking and medications: Quitting smoking can greatly benefit participants' health. However, changes in smoking can lead to changes in how well some medications work. Participants should disclose all medications they are taking. We also recommend that participants discuss any planned or actual changes in how much they smoke with their doctor, especially if they are taking any medications for psychiatric, cardiovascular, or other serious diseases.
14) Wearing the Nicotine Replacement Patch: Participants may experience adverse effects including:
    a. Nervousness
    b. Nausea
    c. Skin irritation
    d. Dizziness
    e. Vomiting
    f. Weakness
    g. Numbing sensation of the hands and feet
    h. Diarrhea
    i. Sleep disturbances
    j. Rapid heartbeat
    k. Headache
    l. Skin discoloration
15) Carbon monoxide sample videos: Video and CO information submitted via text message to a study email address will be transferred to a secure server accessible only to research staff. Although every effort will be made to ensure confidentiality of this information, there is a possible risk that video information could be seen by someone who would recognize a participant. In order to ensure confidentiality, video and CO information will only be identified with the Subject ID number. All videos will be destroyed at the end of the study.

Avoiding Risks to Fetus

If participants choose to be sexually active, they should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. Female participants with child-bearing potential will be tested for pregnancy at the screening visit, before randomization during the Randomization Visit and Visit 77. If a participant becomes pregnant during the study, she will be withdrawn from the study. Approximately 30 days after being withdrawn or having a positive pregnancy test at Visit 77, the research staff will call the participant to confirm her due date. The licensed medical professional will follow-up with the participant after delivery to ask questions about the baby's health.

Expected benefits of participation

There are no immediate benefits from participating in the study. The information obtained from this study may ultimately help the Food and Drug Administration decide how best to regulate tobacco products with the goal of improving public health.

Randomization Visit

This study will use a one week baseline period prior to the Randomization Visit to collect individual difference measures and monitor daily usual-brand smoking behavior using the IVR call system. During the baseline period, participants will not be provided their usual brand cigarettes to smoke by the lab. At the Randomization visit, participants will complete subjective questionnaires, a cue reactivity paradigm and smoking topography. This will last approximately two hours.

Researchers will complete the End of Visit Evaluation Form, which will be entered into REDCap. This will allow the researcher to make note of any problems encountered during the visit, to track which computers were used for which tasks, and to assess the truthfulness of the participant in regards to self-report of tobacco use.

Visit scheduling requirements

Participants will be required to schedule the Randomization Visit between 6 and 21 days after the Screening Visit. The ideal target window is between 6 and 12 days. If the participant does not complete the visit within 21 days, then he/she will not be rescheduled and will be discontinued from the study.

Physiological measures collected, recorded on paper, and entered into REDCap by the interviewer at the end of the visit:

1) BAL
2) Weight
3) Three CO readings (initial visit CO, pre-topography and post-topography)
4) Blood Pressure
5) Heart Rate
6) Urine Pregnancy Test, if applicable

The following assessments will be administered as an interview and entered into REDCap by the interviewer:

1) Concomitant Medications Form
2) Medical Event Form, if applicable, will assess the nature, severity, duration, action taken, and outcome of medical event.
3) Health Changes Questionnaire which will assess any weekly health changes.
4) Timeline Follow Back Questionnaire**,** which will assess other tobacco and nicotine product use as well as alcohol use during the past 14 days.

The following assessment will be administered on paper and kept as a source documents only:

1) BDI, if applicable

The following assessments will be administered using Qualtrics:

1) Respiratory Health Questionnaire, a measure of cough, shortness of breath and other respiratory symptoms
2) Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), a measure of nicotine withdrawal

3) Questionnaire of Smoking Urges-brief scale - Usual Cigarette (QSU; Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991), which measures the urge to smoke
4) Cigarette Evaluation Scale (CES; Westman, Levin, & Rose, 1992), which measures responses to cigarettes (e.g., reward, satisfaction)
5) Environmental and Social Influences on Tobacco Use Questionnaire (adapted from Nondahl, Cruickshanks, & Schubert, 2005), which measures tobacco smoke exposure at home, work and socially
6) Cigarette Purchase Task – Usual Brand Version (Jacobs & Bickel, 1999; MacKillop et al., 2008) which will be used to generate cigarette demand curves. Participants will be asked to report the number of cigarettes that they would consume in a day at various costs. Several indices of demand are generated from the raw values, including demand intensity (consumption at zero price), Omax (maximum amount of money allocated to cigarettes), breakpoint (the first price at which a subject reports zero consumption) and Pmax (the price at which Omax occurs). This task will indicate whether prolonged VLNC cigarette use reduces cigarette demand and increases sensitivity to increases in cigarette costs.
7) Rapid Eating Assessment for Patients (REAP; Gans et al., 2003) which is a measure to assess diet and basic physical activity.

In the event that the Qualtrics website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Qualtrics when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

Puff Topography

Puff Topography, a precise measure of smoking behavior (Brauer et al., 1996; Herning et al., 1981; Robinson & Forbes, 1975), will be used to examine whether prolonged use of the experimental cigarettes affects topography measures that may indicate smoking compensation (Strasser et al., 2007). Puff topography will be assessed using a handheld topography device that provides a valid measurement of puff number, puff volume, inter-puff interval and other indices (Blank et al., 2009). Carbon monoxide readings will be collected before and after puff topography.

Cue Reactivity Computer Task

Cue Reactivity will be assessed to investigate whether prolonged use of VLNC cigarettes extinguishes conditioned effects of smoking-associated stimuli. Reactivity to smoking-related cues will be indexed as the difference between an individual's responding to smoking-related compared to non-smoking pictorial cues. Each trial will consist of a relaxation period, baseline period and the cue presentation, and then a prompt to fill out subjective reactions to viewing the pictures. This procedure will be repeated for up to eight trials. Smoking cues will include smoking-related objects (e.g., a cigarette burning in an ashtray) and contexts (e.g., bar). Non-smoking cues will also include both objects (e.g., a pen and pad of paper) and contexts (e.g., museum). Smoking and non-smoking cue trials will be presented in a counterbalanced order such that no more than two of any one cue trial type will occur consecutively. Multiple cues will be used in random order to avoid habituation to any specific cues over the course of the study.

Biological specimens collected, stored, and entered into CENIC Biosample Collection Platform:

1) First void urine sample for smoking biomarker assessment**:**
   Participants will be asked to bring a urine sample (first void of the day) to the Randomization Visit for biomarker assessment. Samples will be stored at temperatures no more than -20°C. Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota. The

tobacco-specific carcinogen biomarkers are total NNAL and total NNN. We will also assess total nicotine equivalents and minor alkaloids, including anatabine, anabasine, myosmine, and nornicotine. If a participant forgets to bring his/her urine sample, then an on the spot urine sample will be collected.

2) Saliva sample for cotinine assessment:
Participants will be asked to provide two saliva samples during the Randomization Visit for assessment of nicotine metabolite ratio (NMR), an indicator of CYP2A6 enzyme activity. Participants must wait 30 minutes after arrival to the lab before collecting the first saliva sample. During this time participants cannot eat, drink, chew gum or smoke cigarettes. After collecting the sample, provide time for the participant to eat and/or drink before waiting another 30 minutes before collecting the second saliva sample. The second saliva sample must be collected prior to puff topography. Samples will be stored at temperatures no more than -20°C. Saliva samples will be sent regularly to be analyzed and stored at the University of Minnesota.

3) Saliva sample for DNA analysis**:**
Participants will be asked to provide a saliva sample for DNA analysis. The sample will be collected using an OraGene kit. Saliva samples will be sent quarterly to be stored at the University of Minnesota. The DNA sample will be used to determine if there are links between genes and levels of tobacco constituents, behavior, mood, brain functioning, the harmful effects of smoking. Participants who chose not to provide a DNA sample will still be allowed to participate in the study.

Experimental Phase

At the end of the Randomization Visit, participants (N=240) will be randomized equally into one of four experimental conditions. Groups will be stratified by menthol status so there are 50% menthol and 50% non-menthol smokers in each condition. Participants in each condition will be assigned a cigarette that matches their menthol preference.

Experimental Conditions

VLNC Cigarette, nicotine patch	**VLNC Cigarette, no patch**
NNC Cigarette, nicotine patch	**NNC Cigarette, no patch**

Spectrum Cigarettes to be Used in ***Project 1, Study 2: The Combined Impact of Nicotine Replacement and Spectrum Cigarettes***

Condition	TPMF Code	Type*	Specifications Nicotine Yield	Specifications Tar Yield	Specification Range for Nicotine Yield
1	NRC600	CN	0.8 ± 0.15	9 ± 1.5	0.65 - 0.95
1	NRC601	CN-Men	0.8 ± 0.15	9 ± 1.5	0.65 - 0.95
2	NRC102	RN	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04
2	NRC103	RN-Men	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04

*Legend:	
RN	Reduced Nicotine
RN-Men	Reduced Nicotine-Menthol
CN	Conventional Nicotine

CN-Men	Conventional Nicotine-Menthol

The Administrative Core for the Center for the Evaluation of Nicotine in Cigarettes (CENIC) will be responsible for removing all identifying information from cigarettes received from the Research Triangle Institute (RTI), labeling each carton with a blind code, assigning product using this blind code based on the randomization schedule being provided by the CENIC Biostatistics Core, and shipping cigarettes to each site as needed based on recruitment. The site will be responsible for tracking product received and distributed to participants, collecting unused product from participants, and destroying unused open packs. The participants, investigators and study staff will not have knowledge of which product is given to a participant or whether different participants received the same or different product.

Participants will be provided with a 14-day supply of research cigarettes. This will ensure adequate availability of cigarettes in the numerous locations participants may typically keep a supply (home, work, vehicle, etc.) as well as avoid expending the entire supply if they miss a scheduled visit. During the Abstinence Incentive Test, participants will receive a 7-day supply of research cigarettes.

If there is prior knowledge a participant will be missing a visit (i.e. planned vacation, laboratory closure, etc.), then the participant will be provided with an adequate supply of cigarettes to make up for the missed visit(s). The participant will be given a 21-day supply if one visit is going to be missed and a 28-day supply if two visits are going to be missed.

Additionally, participants who are randomized to a nicotine replacement condition will receive a 14-day supply of NicoDerm CQ (or generic equivalent) nicotine replacement patches with doses determined by their baseline cigarettes per day smoking rate. Participants will return unused patches at each visit for product accountability purposes. The NicoDerm patches will be purchased from the University of Pittsburgh's Investigational Drug Service who will conduct an audit of the site's dispensing procedures.

Participants will be instructed to apply a new patch every 24 hours to skin that is dry, clean and hairless (e.g. upper arm). The patches should be worn daily for 16-24 hours. If participants develop vivid dreams or sleep disturbances, they will be told not to wear the patches while sleeping. For the Abstinence Incentive Test, they will be given a 7 –day patch supply and instructed to continue wearing the nicotine replacement patches.

Cigarettes Per Day	Nicotine Patch Dosage
5-19	14 mg
20+	21 mg
If lower dose needed (LMP must decide)	7mg

Product Accountability

Participants will be required to keep track of all the cigarettes provided to them. Therefore, they will be instructed to return all unused cigarettes and empty cigarette packs to the laboratory each week. Because participants are provided with a 14-day supply, they will receive a nominal payment for returning unused product to the lab. Each week participants return $\geq$ 25% of their supply, they will receive a $5.00 credit which will be paid at the end of each applicable visit. This payment is to encourage participants to keep

track of their study cigarettes, minimize hoarding of the study cigarettes, and discourage sharing the study cigarettes with other people. There is no additional incentive for returning the nicotine patches.

Research staff will complete the 'Product Accountability Log' with the participants. Any discrepancies in the product dispensed versus product returned will be discussed and recorded in the log. Empty cigarette packs will not be saved; however, research staff will keep all empty cartons in storage for reference. Unused cigarettes will be re-distributed to the participants during Visits 01-06. At Visit 06, participants will be instructed to abstain from smoking but will be provided with a 7-day supply. If they do lapse during the Abstinence Incentive Test, they will be asked to lapse to their assigned study cigarettes. They will be encouraged each day to re-initiate abstinence.

During the Experimental Phase, if participants lose more than two packs of cigarettes and require an unscheduled visit to the laboratory to supplement their supply, they will be told the next time they lose more than two packs they will have to wait until their next scheduled appointment to receive more cigarettes.

Visit scheduling requirements for the Experimental Phase

REDCap will automatically generate the ideal visit calendar once the participant has been randomized. The perfect scheduling window between each visit is 7 days based on the date of the Randomization Visit. If a participant misses a visit and is not able to reschedule during the window, that visit will not be 'made-up' in the future. All measures that were not completed will be considered missing data and will not be collected during future visits. If a visit mistakenly occurs outside of the designated window, this is a protocol deviation. A 'Non-Medical Event Form' will need to be completed and tracked in REDCap. If a participant is not able to attend Visit 06, then it should be rescheduled even if it is outside of the scheduling window. This will be documented as a protocol deviation.

Visits 01, 03, 04, and 05 Procedures

Physiological Measures Collected, recorded on paper, and entered into REDCap by the interviewer at the end of the visit:

1) BAL
2) Weight
3) CO
4) Blood Pressure
5) Heart Rate

The following assessments will be administered as an interview and will be entered into REDCap by the interviewer:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Timeline Follow Back Questionnaire

The following assessment will be administered on paper and kept as a source document only:

1) BDI, if applicable

The following assessments will be administered using Qualtrics:

1) Respiratory Health Questionnaire
2) MNWS
3) QSU brief - Usual Brand Cigarette

4) QSU brief– Study Cigarette
5) Cigarette Evaluation Scale

In the event that the Qualtrics website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Qualtrics when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

Biological specimens collected, stored, and entered into CENIC Biosamples Collection Platform:

1) Spot urine sample for assessing total nicotine equivalents and minor alkaloids to determine product compliance

Cue Reactivity In Vivo Task (Week 05 only)

Participants will be exposed to an *in vivo* smoking cue (i.e., the assigned study cigarette). A tray with a plastic cover will be placed on the desk in front of them, and they will be instructed not to touch the tray. After 20 s, they will be instructed to pick up the cover thereby revealing their pack of study cigarettes, a lighter, and an ashtray. They will be told to remove a cigarette from the box and to light it without putting it in their mouth by holding it in the flame for several seconds until the tobacco begins to burn. Next, they will be told to put down the lighter, hold the cigarette in a comfortable manner, and look at it. Thirty seconds after lighting the cigarette, the will rate their urge to smoke. Self-reported urge to smoke will be assessed using a rating scale ranging from 0 (*absolutely no urge to smoke at all*) to 100 (*strongest urge to smoke I've ever experienced*). This single-item scale has proven sensitive to a wide range of craving experiences (Juliano & Brandon, 1998; Sayette et al., 2001). Participants will be video recorded during the in vivo task so that facial expressions can be coded in the future

Visits 02 and 06 Procedures

Physiological measures collected, recorded on paper, and entered into REDCap by interviewer at the end of the visit:

1) BAL
2) Weight
3) Three CO readings (initial visit CO, pre-topography and post-topography)
4) Blood Pressure
5) Heart Rate
6) Urine sample for drug test (Week 6 only)

The following assessments will be administered as an interview and will be entered into REDCap by the interviewer:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Timeline Follow Back Questionnaire
5) Drug Use Questionnaire - 1 month version (Visit 06 only)

The following assessment will be administered on paper and kept as a source documents only:

1) BDI, if applicable

The following assessments will be administered using Qualtrics:

1) Respiratory Health Questionnaire
2) MNWS

3) QSU brief - Usual Cigarette
4) QSU brief – Study Cigarette
5) FTND
6) Cigarette Evaluation Scale
7) Perceived Health Risks Questionnaire
8) Smoking Stages of Change Algorithm and Contemplation Ladder
9) Cigarette Purchase Task - Usual Brand Cigarette Version
10) Cigarette Purchase Task – Study Cigarette Version
11) Rapid Eating Assessment for Patients
12) PANAS
13) Perceived Stress Scale – 4 item
14) Alcohol Use Questionnaire -1 month version (Visit 06 only)
15) Environmental and Social Influences on Tobacco Use Questionnaire (Visit 06 only)
16) CESD (Visit 06 only)
17) WISDM-Brief (Visit 06 only)

In the event that the Qualtrics website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Qualtrics when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

Participants will also complete the following tasks

1) Puff Topography
2) Cue Reactivity

Biological specimens collected, stored, and entered into CENIC Biosamples Collection Platform:

1) Spot urine sample for assessing total nicotine equivalents and minor alkaloids to determine product compliance.
2) First void urine sample for smoking biomarker assessment: Participants will be asked to bring a urine sample (first void of the day) for biomarker assessment. Samples will be stored at temperatures no more than -20°C. Urine samples will be sent quarterly to be analyzed and stored at the University of Minnesota. The tobacco-specific carcinogen biomarkers are total NNAL and total NNN. We will also assess total nicotine equivalents and minor alkaloids, including anatabine, anabasine, myosmine, and nornicotine. If a participant forgets to bring his/her urine sample, then an on the spot urine sample will be collected.

<u>Interactive Voice Response System</u>

Participants will continue to use the IVR system on a daily basis throughout the experimental period to record the number of study cigarettes smoked per day and use of non-study cigarettes. During the first week after randomization and during the Abstinence Incentive Test the IVR system will collect information about withdrawal symptoms.

<u>Product and Procedures Compliance Review Sessions</u>

Participants will be counseled weekly about their use of the study cigarettes. They will be asked about any concerns or obstacles associated with using the study cigarettes and nicotine replacement patches (if applicable). The importance of honest self-reporting will be stressed. If difficulties are encountered, participants will be asked why they think they are experiencing difficulties (e.g., taste, withdrawal symptoms) and to problem-solve how to deal with these difficulties in order to meet the protocol requirements.

Additionally, participants will be counseled about their nicotine patch usage, IVR completion, visit attendance, task engagement and product accountability.

At the end of Visit 06 compliance review session, participants will be encouraged not to smoke for the next week and will be told they will receive a monetary incentive each day they achieve abstinence. Participants will be provided with the 'Clearing the Air' Manual and will troubleshoot any concerns they may have about being abstinent from smoking during the next week.

Abstinence Incentive Test

After Visit 06, participants will be instructed to try to abstain from all combustible tobacco products including cigarettes, cigars, little cigars, cigarillos, hookah, bidis and marijuana for the seven days. After completion of this visit, subjects will be sent home with a piCO+ CO monitor and study cell phone to complete the at-home abstinence incentive tests. Participants will use a cell phone to record and text videos of themselves taking carbon monoxide readings. They will be required to submit CO videos twice per day, one video between 8AM-12PM and one video between 4-8PM (+/- 1 hour for each submission window). The study cell phones will be programmed with two daily alerts (10AM; 6PM) to remind them to complete their videos. Staff will review these videos to confirm abstinence. To be verified as abstinent, participants must achieve a CO of $\leq$ 7 ppm or a 50% reduction from the previous CO reading. Both videos must meet criteria in order to earn the daily incentive. Each abstinent sample will be reinforced according to a descending schedule of reinforcement described below.

Abstinence Day 1 (Visit 71)	**$80.00**
Abstinence Day 2	$40.00
Abstinence Day 3	$20.00
Abstinence Day 4	$10.00
Abstinence Day 5	$5.00
Abstinence Day 6	$2.50
Abstinence Day 7 (Visit 77)	$0.00
Total	**$157.50**

If a participant fails to meet the CO criteria or forgets to send a video, then he/she will not be earn the monetary incentive for that day. Participants will be instructed that if they do relapse to smoking during the Abstinence Incentive Test, then they should smoke their assigned study cigarette and not their usual brand. Even after a lapse, participants will be encouraged to re-initiate abstinence.

Visit scheduling requirements for the Abstinence Incentive Test

The participant must complete the Visit 71 between 20-28 hours after Visit 06. Additionally, he/she must return to the lab exactly 6 days after visit 71 to complete Visit 77.

Visit 71 Procedures

Physiological measures collected, recorded on paper, and entered into REDCap by interviewer at the end of the visit:

1) BAL
2) CO reading
3) Blood Pressure
4) Heart Rate

The following assessments will be administered as an interview and will be entered into REDCap by the interviewer:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Timeline Follow Back Questionnaire

The following assessment will be administered on paper and kept as a source documents only:

1) BDI, if applicable

The following assessments will be administered using Qualtrics:

1) Respiratory Health Questionnaire
2) MNWS
3) QSU brief - Usual Cigarette
4) QSU brief – Study Cigarette
5) PANAS
6) PSS-4
7) Cigarette Purchase Task - Usual Brand Cigarette Version
8) Cigarette Purchase Task – Study Cigarette Version

In the event that the Qualtrics website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Qualtrics when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

Biological specimens collected, stored, and entered into CENIC Biosamples Collection Platform:

1) Spot urine sample for assessing total nicotine equivalents and minor alkaloids to determine product compliance

Visit 77 Procedures

Physiological measures collected, recorded on paper, and entered into REDCap by interviewer at the end of the visit:

1) BAL
2) Weight
3) CO reading
4) Blood Pressure
5) Heart Rate
6) Urine sample for pregnancy test (if applicable)

The following assessments will be administered as an interview and will be entered into REDCap by the interviewer:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Timeline Follow Back Questionnaire

The following assessment will be administered on paper and kept as a source documents only:

1) BDI, if applicable

The following assessments will be administered using Qualtrics:

1) Respiratory Health Questionnaire
2) MNWS
3) QSU brief - Usual Cigarette
4) QSU brief – Study Cigarette
5) PANAS
6) PSS-4
7) CESD

In the event that the Qualtrics website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Qualtrics when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered into REDCap.

Biological specimens collected, stored, and entered into CENIC Biosample Collection Platform:

1) Spot urine sample for assessing total nicotine equivalents and minor alkaloids to determine product compliance

Interactive Voice Response System

Participants will continue to use the IVR system on a daily basis throughout the Abstinence Incentive Test to record the number of study and non-study cigarettes smoked each day as well as assess withdrawal symptoms.

End of Study Procedures

After a participant has completed all study procedures and has been paid for participation the research assistant should read the following script and give the participant the *Clearing the Air Manual (if they need another copy).*

"Before you go, we want to encourage you to try to continue to be abstinent as long as possible. Although the study is over and abstinence is not required, you may find it easier to quit as a result of your participation. We would like to provide you with some resources should you decide to try to abstain from smoking (give "Clearing the Air" and hotline information). Please also feel free to consult with your physician and use any medications he/she deems appropriate. We will call you in approximately 30 days to ask about your smoking since leaving the study. There is no right answer and we know how difficult quitting can be. Please just answer honestly. The call will take less than 5 minutes, and we will compensate you for your time by giving you another $10. Thanks again for your participation."

The following assessments will be administered using Qualtrics:

1) End of Study Questionnaire
2) Study Evaluation Questionnaire

30 Day Follow up Phone Call

Participants will receive a follow-up phone call between 25 and 35 days after the abstinence assessment session to assess their smoking patterns. The phone questionnaire will last less than five minutes. The questionnaire will ask if the participant is still smoking, how much and whether he/she has attempted to quit smoking since the end of the study. Additionally, any Medical Event Forms that remain open from the last session will be discussed. If the participant became pregnant during the study, this would have been recorded as a medical event. During this phone call, the research assistant will confirm her due date.

This event will remain open until delivery. At that time the licensed medical professional will contact the participant to ask a few questions about the baby's health and will update the Medical Event Form.

Once a participant has completed all study procedures and all open events have been closed, the PI will review the participant's binder and sign a form indicating study completion for that participant.

Study Debriefing

After data collection is complete, participants will receive a letter telling them which condition they were randomized into and the results of the study thus far.

Data Storage

Data will be stored locally at each site and at the University of Minnesota Masonic Cancer Center's Bioinformatics Core for at least 7 years after study completion.

Participant Compensation

Screening- Eligibility Only	**$25.00**
Screening- Additional Baseline Measures	$25.00
Randomization Visit	$75.00
Visit 01, 03, 04, 05, 71, 77 ($25/visit)	$150.00
Visit 02, 06 ($75/visit)	$150.00
30 Day Follow Up Call	$10.00
Total	$435.00

Participants are free to discontinue at any time and will receive compensation for the sessions completed at the same rate listed above. However, they will not receive the fixed bonus for attending all sessions.

Incentives

Participants can earn FIXED incentives based on performance.

IVR Calls ($1.00/completed call; $10 for full week)	Up to $136.00
Fixed bonus for attending all sessions	$100.00
Abstinence Incentive Test	Up to $157.50
Returned Packs	Up to $35.00
Total	$428.50

Participants can earn VARIABLE incentives based on performance and a random drawing (described below in detail)

Incentive for Compliance, Retention, and Honesty	Average of $100, but variable

Participants will also be able to select a $1 Pennsylvania Lottery scratch-off ticket from a basket if they arrive on time (within 15 minutes) and have not rescheduled their appointments. If the participant is not on time or has to reschedule, he/she will not be penalized from the completion bonus but would miss the opportunity to select a lottery ticket from the basket. They can earn up to ten $1 Pennsylvania Lottery scratch-off tickets. During the experimental phase, participants will receive a $5 bonus at each visit (excluding Visit 71) where they bring back 25% or more of their cigarette supply from the previous visit (should be a maximum bonus of $35 across all possible visits).

Incentivized Compliance, Honesty and Retention Program

A procedure has been developed to help participants achieve better compliance to the study product while at the same time encouraging honest self-reported tobacco use and study retention. Briefly, participants will receive tickets for being compliant with study product use, being honest about product use, and attending their sessions. These tickets will be entered together into a monthly drawing for prizes. Only tickets that are "validated" will be eligible for prizes. Validation is described below. This procedure (referred to as the "Variable Incentive Program" relies on a probabilistic or variable contingency relationship between the target behaviors and delivery of the incentives. Variable ratio schedules of reinforcement are well-known to produce high rates of behavior.

Participants will receive a total of five tickets for each visit they attend after randomization (Visits 01-77). One ticket is for honestly self-reporting their tobacco use, one for attending the visit and three for being compliant by not using non-study nicotine/tobacco products. In total, participants could earn 40 valid tickets across the eight visits.

The attendance ticket will be valid for all participants attending their scheduled session.

The compliance tickets will be validated using a semi-bogus pipeline procedure. Tickets that are selected for subjects in the VLNC cigarette groups will be biochemically verified for compliance to the study product by testing for cotinine, total nicotine equivalents or minor alkaloid levels in their weekly spot urine samples. However, subjects in the NNC cigarette groups will not have their urine samples biochemically verified because it is currently not feasible to detect non-compliance based on biomarkers. Instead, if a compliance ticket from someone in one of the NNC cigarette groups is selected, then a urine sample from the corresponding VLNC cigarette group would be randomly selected and analyzed in its place. If this ticket is biochemically verified for compliance to the study product, then the subject in the NNC cigarette group would receive the monetary incentive. This semi-bogus pipeline procedure will help to minimize between group differences in the number of incentives awarded since the alternative would be to have all NNC group tickets be considered valid. Additionally, this will help to maintain the blind for research staff so they will not be able to determine which subjects are in the NNC cigarette groups.

The honesty ticket will be validated if the biomarker data are consistent with the participant's self-reported tobacco use. As with compliance tickets, honesty tickets will rely on a semi-bogus pipeline procedure.

If the biochemical verification data are not available by the first of the month, then all compliance and honestly tickets will be deemed valid.

Tickets as described to participants:

> **Honesty Ticket**: *This ticket is for accurately reporting when you used study and non-study products. We will compare what you tell us to what is in the urine you give us while in the lab. If your urine matches what you tell us, the ticket would be valid. If you slip and use another product, just tell us. This ticket is for being honest, not for being perfect. If that ticket is later drawn for a prize, you will only win the prize if your ticket is valid.*
>
> **Attendance Ticket**: *This ticket is for attending the visit. If you come to the visit and do your best to answer the questions, this ticket will be valid.*
>
> **Compliance Ticket**: *These tickets are for using the study product we assigned to you and not using other nicotine/tobacco products. We know this is hard, so we are giving up to three tickets for doing a good job. This is based entirely on the urine you give us (what you tell us does not matter). The more compliant you are (according to your urine) the more tickets we will "validate." So even*

if you "slip", try to go back to using the study product as soon as possible. You might still get tickets validated!

Each month we will ship all 1ml urine samples accumulated from the 16th of the preceding month up to and including the 15th of that month. Those samples will be analyzed for cotinine, total nicotine equivalents (TNEs) and minor alkaloids by the end of the month. Drawings will be conducted on the 1st of each month. All available biochemical data will be used to validate Honesty and Compliance tickets. Validation will be performed by staff who have no participant interaction and are not blind to condition.

Each drawing will be independent (without replacement); consequently, some participants will not win a prize and others may win more than one during the study if more than one of their tickets is drawn. After confirming winners, the remaining tickets from each month will be discarded (i.e., tickets will only be entered into one drawing). The monthly prize amounts are detailed below. If the ticket drawn is valid, then that person will receive the prize. If the ticket drawn is not valid, then another ticket will be drawn until a winner is determined.

We estimate, based on the 2 years we think it will take to complete this study, that participants will win an average of approximately $100 in prizes.

Grand Prize (1): $750 cash

Second Prize (1): $200 cash

Third Prize (5): $10 cash

Please review the *P1S2 Variable Incentive Program PowerPoint* for additional information.

Quit Attempts During the Study

At each weekly session, we will ask the participant if he/she is currently abstaining from smoking with the intention of quitting. If the answer is no, then we will also ask if he/she is planning to quit smoking prior to his/her next scheduled visit.

If a Participant is Currently Abstaining from Smoking with the Intention to Quit:

- Encourage participant to continue abstaining from smoking
- Schedule the participant for normal weekly visits, but no puff topography
- Provide the participant with the '*Clearing the Air*' manual and local smoking cessation resources
- Give the participant the option to take home study product rather than require him/her to take the product
- If the participant choses to take home the study product have him/her sign a form acknowledging that cigarette availability could be detrimental to the quit attempt. Recommend that he/she puts the product "away" at home as to avoid unwanted cues to smoke.
- If the participant chooses not to take home the study product, have him/her contact the lab if he/she lapses and would like to pick up or be mailed the study product prior to his/her next visit.

If a Participant is Planning to Quit Smoking, but has not initiated the quit attempt

- Ask if he/she has identified a target quit date and, if so, what that target date is
- Provide the participant with the '*Clearing the Air*' manual and local smoking cessation resources
- Provide the participant with the study product as usual. Recommend that on the target date he/she puts the product "away" at home as to avoid unwanted cues to smoke.

Adverse Events and Withdrawal or Monitoring of Participants

Identifying Adverse Events

While participating in the trial, adverse events and concomitant medications will be assessed at every study visit and vital signs and carbon monoxide will be obtained. Medical events will typically be identified during the administration of the Health Changes Questionnaire and Respiratory Health Questionnaire, and in some cases during the administration of the CESD. Other events may be identified from physiological study measures or by spontaneous reports during non-scheduled assessments.

Questionnaire items that will be reviewed:

- Health Changes Questionnaire: If the participant answers **'YES'** to **Questions 1, 2, 3b** or **3c** , the interviewer should administer the 'Medical Event Form.'
    1) ***Have you had any negative changes in your physical or mental health since your last visit?***
    2) ***Have you had any changes in medication since your last visit?***
    3) *Since your last visit, have you received any form of medical care?*
        a. *Have you received any preventive care?*
        b. ***Have you needed to seek immediate medical care, gone to the emergency room, or been hospitalized since your last visit?***
        c. ***Have you received any care for an illness, injury, or other medical complaint that did not require emergency care?***
        d. *Have you received any follow-up care?*
- Respiratory Health Questionnaire: If the participant indicates **'YES'** to **Question 5** regarding having a cold or flu the interviewer should administer the 'Medical Event Form.'
- CESD: If the participant **scores 16 or higher and are not already being monitored for depression**, a 'Medical Event Form' should be completed and the LMP will provide information regarding follow-up. If there is already an open event, information will be added to the existing 'Medical Events Form.'

Physiological data that will be reviewed:

- CO level: The 'Medical Event Form' should be completed if the average of two consecutive measurements in the same visit is:
    - CO is greater than 50 ppm if CO at Randomization is < 20 ppm.
    - CO is greater than 60 ppm if CO at Randomization is 20 – 34 ppm.
    - CO is greater than 70 ppm if CO at Randomization is 35 – 49 ppm.
    - CO is greater than 80 ppm if CO at Randomization is 50 – 64 ppm.
    - CO is greater than 90 ppm if CO at Randomization is 65 – 80 ppm.
- Blood Pressure:
    - The 'Medical Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual blood pressure measurement during the same visit is **at or above 160/100**
    - The 'Medical Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual blood pressure measurement during the same visit **is below 90/50 and the participant is experiencing symptoms** listed on the 'Blood Pressure and Heart Rate Symptom Checklist.'
- Heart Rate:
    - The 'Medical Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual heart rate measurement during the same visit is **at or above 105 bpm.**
    - The 'Medical Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual heart rate measurement during

the same visit is **below 45 bpm <u>and</u> the participant is experiencing symptoms** listed on the 'Blood Pressure and Heart Rate Symptom Checklist.'

<u>Management of SAEs and Other Study Risks</u>

The site medical professional will review all AEs. A study participant may be discontinued from the study if the medical professional and/or PI determine it is the best decision in order to protect the safety of a participant. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an AE/SAE, the participant will have appropriate follow-up medical monitoring. The participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study cigarettes. Any AE that remains open will be reviewed and closed at the 30 day follow-up interview.

Reporting of SAEs to the IRB, FDA, and NIDA

Serious adverse events (SAEs) as defined in 21 CFR 312.32 (death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage (devices), other serious (important medical outcomes)) that are related or possibly related to study participation will be reported to the Administrative Core, all site IRBs, the NIDA Scientific Officer (Ivan Montoya, MD), the NIDA Project Officer (Kevin Walton, PhD), FDA, and the Data Safety and Monitoring Board. All Site IRBs require that fatalities related to the study be reported within 24 hours, that all other SAEs be reported within 5 business days. Reports of all SAEs will also be documented within NIDA's SAE data monitoring system, or SAETRS, within 72 hours.

Reporting of IRB Actions to NIDA

Actions taken by the local IRBs in response to SAEs will be reported to NIDA in the annual noncompetitive continuation application, as will reports of changes or amendments to the protocol as a result of an SAE. Recommendation for trial discontinuation, for significant changes or amendments to the protocol, or other significant findings as a result of an SAE will be reported immediately to the NIDA Scientific Officer (Ivan Montoya, MD) and Project Officer (Kevin Walton, PhD) by the Project PI.

Reporting Changes or Amendments to the Protocol

Any changes or amendments to the protocol made in response to adverse events/SAEs will be discussed with Eric Donny, PhD and Dorothy Hatsukami, PhD, and then requested in writing to the IRB, which will then grant or deny permission to make the requested change in protocol. The DSMB and FDA will be notified about any significant changes to the protocol. NIDA will be informed of any approved changes in protocol by documentation in the noncompetitive continuation application. Changes that significantly alter the scope of the research or the ability of the research to achieve its specific aims will be submitted to Eric Donny, PhD and Dorothy Hatsukami, PhD, the DSMB, FDA, and NIDA for approval prior to implementation.

Withdrawal or Monitoring of Participants

For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1) <u>Cardiovascular disease (CVD) event</u>: Typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
2) <u>DVT/PE</u> (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).

3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
5) Pregnancy: If participant indicates she is pregnant or has a positive pregnancy test at the Randomization Visit, she will be withdrawn from the study, and this event will remain open until delivery. At that time the licensed medical professional will contact the participant to ask a few questions about the baby's health and will update the open 'Medical Event Form'. A positive pregnancy test at Visit 77 will trigger a 'Medical Event Form' to be completed but will not result in withdrawal since she is no longer receiving study product.
6) Expired breath carbon monoxide increase: A participant will be withdrawn from the study if the average of the 2 (or 3) CO readings is 100 ppm or greater.
7) Marked increase in smoking: A participant will be withdrawn from the study if he/she meets **BOTH** of the following criteria for two consecutive weeks
    a. Cigarette per day increase: The average CPD increases by more than 100% from the average CPD during baseline.
    b. Expired breath carbon monoxide increase: if the average of the 2 (or 3) CO readings is:
        i. CO is greater than 50 ppm if CO at Randomization is < 20 ppm.
        ii. CO is greater than 60 ppm if CO at Randomization is 20 – 34 ppm.
        iii. CO is greater than 70 ppm if CO at Randomization is 35 – 49 ppm.
        iv. CO is greater than 80 ppm if CO at Randomization is 50 – 64 ppm.
        v. CO is greater than 90 ppm if CO at Randomization is 65 – 80 ppm.

The following will be monitored and can lead to the participant being withdrawn by the PI or Licensed Medical Professional:

1) Cigarettes per day increase: Continued participation will be evaluated by the site PI if the average number of cigarettes per day (CPD) increases by more than 100% from the average CPD during baseline as determined by CPD on the Timeline Follow Back at Randomization.
2) Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-enrollment: 1) BP is at or above 160/100 or below 90/50, or 2) HR is at or above 105 bpm or below 45 bpm a manual blood pressure and heart rate measurement will be taken after 10 minutes have passed. If the manual reading is still out of range, a 'Blood Pressure and Heart Rate Symptom Checklist' and 'Medical Event Form' will be completed, and the participant will be monitored by the medical professional.
3) Expired breath Carbon Monoxide increase: Two CO readings will be performed each time a CO reading is necessary (initial, pre, or post-topography). If the 2nd CO reading differs from the 1st reading by more than 2ppm, a 3rd CO reading should be taken. A 'Medical Event Form' will be completed and the participant will be monitored by the medical professional if the average of the 2 (or 3) CO readings is:
    a. CO is greater than 50 ppm if CO at Randomization is < 20 ppm.
    b. CO is greater than 60 ppm if CO at Randomization is 20 – 34 ppm.
    c. CO is greater than 70 ppm if CO at Randomization is 35 – 49 ppm.
    d. CO is greater than 80 ppm if CO at Randomization is 50 – 64 ppm.
    e. CO is greater than 90 ppm if CO at Randomization is 65 – 80 ppm.

4) Medication changes: If a participant begins taking any of the exclusionary medications or other medications that could potentially have a smoking-drug interaction post- enrollment, the LMP will determine how best to monitor and minimize potential risks (including withdrawal if warranted). We will also recommend that a letter be sent to the participant's physician (with their consent), making them aware of the potential changes in smoking that could occur as a result of participation in the study.
5) Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical professional to determine whether continued participation in the study is appropriate.
6) If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, etc., then the PI can withdraw him/her from the study at the PI's discretion.
7) If a participant fails to attend his/her Randomization Visit within the 21-day allowable visit window, he/she will not be eligible to reschedule this visit or continue participation in the study.
8) If there is reason to believe the participant is sharing large quantities of the study product with other people.

Investigational Tobacco Product

The Co-Directors of this Center grant, Dr. Donny and Hatsukami, have received an Investigational Tobacco Product (ITP) application to the FDA to cover the experimental cigarettes being used in this study.

Certificate of Confidentiality

To help protect the participant's privacy, Dr. Donny has applied for a Certificate of Confidentiality from the National Institutes of Health. With this certificate, the researchers cannot be forced to disclose information that may identify the participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the participants, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

The Certificate of Confidentiality does not prevent the participant or a member of their family from voluntarily releasing information about themselves and their involvement in the research. If an insurer, employer or other person obtains the participant's written consent to receive research information, then the researcher may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without consent, information that would identify the individual as a participant of the research project in instances such as evidence of child abuse or a participant's threatened violence to self or others.

Outcome Variables

Primary Outcome Variables:

- Number of cigarettes smoked per day at Visit 06
    - Study cigarettes
    - Combined study and non-study cigarettes

Secondary Outcome Variables:

- Measures of compliance: non-study cigarette use, drop-out rate

- Measures of discomfort/dysfunction: MNWS, PANAS, QSU, PSS-4, CESD
- Measures of other health-related behaviors: breath alcohol, urine drug screen, Alcohol Use Questionnaire, Drug Use Questionnaire, weight
- Measures of nicotine/tobacco dependence: FTND, WISDM
- Measures of tobacco exposure: CO, total nicotine equivalents, NNN, NNAL, minor alkaloids
- Measures of smoking context: Environmental and Social Influences on Tobacco Use
- Measures of intention to quit: Stages of Change, Contemplation Ladder
- Measures of compensatory smoking: puff topography
- Measures of other tobacco use: TLFB-other tobacco
- Measures of cigarette characteristics: CES, Cigarette Purchase Task
- Measures of cardiovascular function: heart rate, blood pressure
- Measures of perceived risk: Perceived Health Risk Questionnaire
- Measures of the ability to abstain from smoking: Time to first lapse, total number of abstinent days, continuous 7-day biochemically verified abstinence
- Measures of cue reactivity: computer task and in vivo task

Statistical Approach

This study will use a 2x2 factorial design to test the combined effect of VLNC cigarettes and transdermal nicotine patch. We will consider the main effect for each factor along with their interaction. The primary outcome will be cigarettes per day but biomarkers of exposure, measures of dependence, discomfort, compensatory smoking and other health-related outcomes will also be considered. Specifics of our data analytic approach for the primary and secondary outcomes can be found below but we first provide the basic principles that will guide the analysis for all endpoints.

(1) Baseline characteristics including demographics and smoking history will be compared between the treatment groups to identify any baseline imbalances after randomization. Discrete variables will be summarized by frequencies and percentages and compared using the Chi-squared test or Fisher's exact test, as appropriate. Continuous covariates will be summarized by the mean, standard deviation, median and range and compared by one-way ANOVA.

(2) Continuous outcomes will be summarized by the mean, standard deviation, median and range, while categorical outcomes will be summarized by frequencies and percentages. Skewed continuous outcomes will be log-transformed or square root-transformed as appropriate; for example we conventionally analyze cotinine on log scale.

(3) We expect groups to, on average, be balanced for important baseline characteristics due to randomization. Therefore, our primary analysis for all endpoints will only adjust for the baseline value of that endpoint (for precision). However, a secondary analysis will be completed adjusting for age, sex and race, along with any other covariates that differ across treatment groups at baseline with a p-value less than 0.20.

(4) Our primary analysis will follow the intent-to-treat principle, which analyzes subjects based on their randomized treatment assignment regardless of compliance to their randomized treatment assignment. Some level of non-compliance is inevitable in this study. We will compare baseline characteristics between compliers and non-compliers to identify baseline characteristics associated with non-compliance and secondary analyses will be completed to estimate the effect of VLNC and transdermal nicotine patch accounting for non-compliance (Little et al. 2009).

(5) All analyses will be completed using SAS (version 9.2 or 9.3) or R. P-values less than 0.05 will be considered statistically significant.

Our primary endpoint, cigarettes per day at 6 weeks, will be summarized by treatment group and analyzed using linear regression adjusting for cigarettes per day at baseline. The model will include dummy variables for VLNC cigarettes and transdermal nicotine patch, their interaction and a linear term for baseline cigarettes per day. A secondary analysis of the primary endpoint will be completed that also adjusts for age, sex and race, along with any other covariates that differ across treatment groups at baseline with a p-value less than 0.20. Finally, cigarettes per day will be analyzed using a linear mixed model to evaluate trends in the difference in the number of cigarettes per day over time.

Secondary endpoints will be analyzed following the same approach as the primary endpoint. The primary analysis of our secondary endpoints will use linear regression and adjust only for the baseline value. Secondary analyses will consist of an adjusted analysis and a repeated measures analysis using a linear mixed model. In addition, we will also complete pre-planned subgroup analysis by sex (men vs. women), race (white vs. black) and menthol status (non-menthol versus menthol).

Power Analysis

We will enroll 240 subjects in a 2x2 factorial design. Based on our experience with CENIC Project 1, Study 1, we will conservatively assume 10% attrition (i.e. 90% of subjects completing the study), resulting in 206 completers. A 2x2 factorial design with 206 subjects will provide 80% (90%) power to detect an effect size of 0.383 (0.443) for the main effects and an effect size of 0.762 (0.883) for the interaction with a type-I error rate of 0.05. Therefore, our design is adequately powered to detect the effect of VLNC cigarettes observed by Hatsukami et al. (2010) on cigarettes per day (0.991), cotinine (2.096), FTND (0.603) and withdrawal (0.512) and the effect of transdermal nicotine patch observed by Donny and Jones (2009) on cigarettes per day (0.785).

Subject Identifier

The subject identifier is an alpha-numeric combination. Example: D-A001 would be University of Pittsburgh's first subject.

Project Identifier:
D= Project 1, Study 2

Site Identifier:
A = University of Pittsburgh

Subject ID:
001-899

Data Collection Time Points Identification Numbers:
92= Screening/Baseline Visit
00= Randomization
01= Week 1 visit
02= Week 2 visit
03= Week 3 visit
04= Week 4 visit
05= Week 5 visit
06= Week 6 visit
71= Abstinence Incentive Day 1
72= Abstinence Incentive Day 2

73= Abstinence Incentive Day 3
74= Abstinence Incentive Day 4
75= Abstinence Incentive Day 5
76= Abstinence Incentive Day 6
77= Abstinence Incentive Day 7
30= 30 day follow-up phone call
99= Unscheduled visit

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