Supplementary Online Content

Cho YJ, Mehta T, Hinton A, et al. e-Cigarette nicotine delivery among young adults by nicotine form, concentration, and flavor: a crossover randomized clinical trial. *JAMA Netw Open*. 2024;7(8):e2426702. doi:10.1001/jamanetworkopen.2024.26702

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. Ingredients of the Investigational Tobacco Products

ITP Name	Dominant Nicotine Form	–(-)Nicotine (mg/g)	Flavoring	Benzoic acid (mg/g)	Glycerol (mg/g)	Propylene Glycol (mg/g)
T5FB	Freebase	50	Tobacco (Ghost Town[b])	None	700	300
T5NS	Salt-based[a]			37.65		
T1FB	Freebase	10		None		
T1NS	Salt-based			7.53		
M5FB	Freebase	50	Menthol (Yeti[a])	None	700	300
M5NS	Salt-based			37.65		
M1FB	Freebase	10		None		
M1NS	Salt-based			7.53		

[a] Nicotine was protonated with a 2% molar excess of benzoic acid

[b] Ghost Town and Yeti are brand names for the ITPs provided to us by Flagship Vapor.

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eTable 2. Theoretical and measured ingredients in the investigational tobacco products; mean (standard deviation) for replicates (n=3) except for freebase fraction (n=1 pH determination)

Sample ID	Nicotine (% w/w)[a,b]		Freebase Nicotine (% of Total Nicotine)[c]		Propylene Glycol (% w/w)[b]		Glycerol (% w/w)[b]		Menthol (% w/w)[b]	
	Theoretical	Measured	Theoretical	Measured	Theoretical	Measured	Theoretical	Measured	Theoretical	Measured
T5FB	5.00	5.05 (0.02)	100	98.1	30.00	31.35 (0.16)	60.00	59.53 (0.14)	0	ND
T5NS	5.00	4.99 (0.05)	0	0.3	30.00	29.87 (0.20)	60.00	56.19 (0.37)	0	ND
T1FB	1.00	0.97 (0.00)	100	94.3	30.00	32.52 (0.12)	60.00	61.71 (0.48)	0	ND
T1NS	1.00	0.97 (0.00)	0	0.2	30.00	32.16 (0.13)	60.00	60.44 (0.22)	0	ND
M5FB	5.00	5.09 (0.02)	100	98.6	30.00	28.63 (0.10)	60.00	59.96 (0.18)	1.00	0.93 (0.00)
M5NS	5.00	5.05 (0.02)	0	0.2	30.00	27.17 (0.14)	60.00	56.74 (0.22)	1.00	0.83 (0.00)
M1FB	1.00	1.01 (0.00)	100	95.7	30.00	29.88 (0.22)	60.00	62.45 (0.20)	1.00	0.97 (0.00)
M1NS	1.00	0.98 (0.00)	0	0.3	30.00	29.47 (0.08)	60.00	61.55 (0.26)	1.00	0.70 (0.03)

[a] % (w/w) = weight of chemical / weight of e-liquid.

[b] Analyzed using quantitative nuclear magnetic resonance as described in Crenshaw et al., 2016.[1]

[c] 10g of HPLC grade deionized water was added to 1g of e-liquid solution. The mixture was stirred for 15 minutes and the pH was measured. The freebase fraction was calculated using the Henderson-Hasselbalch equation.

ND = not detected

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eTable 3. Participant Characteristics and Tobacco Use History by Number of Visit Preference

	5 Visits (n=21) Mean (SD) or No. (%)	**9 Visits** (n=66) Mean (SD) or No. (%)	p-value
Age	21.9 (1.0)	22.5 (1.4)	0.05
Female sex assigned at birth	12 (57.1%)	39 (59.1%)	0.87
Race/ethnicity[a]			0.91
Hispanic	1 (4.8%)	5 (7.6%)	
Non-Hispanic Black	1 (4.8%)	3 (4.6%)	
Non-Hispanic White	16 (76.2%)	52 (78.8%)	
Other (e.g., multiple races)	3 (14.3%)	6 (9.1%)	
E-cigarette use characteristics			
Days of use during the past 30 days	28.6 (3.2)	27.0 (6.8)	0.71
Years of regular e-cigarette use[b]	3.4 (2.2)	3.3 (2.1)	0.74
Current regular e-cigarette use[b]	21 (100.0%)	63 (96.9%)	1.00
Average Puffs per Day	68.8 (42.3)	82.8 (104.6)	0.74
Flavor[c]			0.38
Tobacco	0 (0.0%)	0 (0.0%)	
Menthol or Mint	10 (47.6%)	24 (36.9%)	
Other flavor	11 (52.4%)	41 (63.1%)	
Nicotine Form[c]			0.59
Nicotine Salts	15 (71.4%)	51 (77.3%)	
Unknown	6 (28.6%)	15 (22.7%)	
Nicotine Concentration, %[c]			
Other tobacco use characteristics			
Ever smoking of a cigarette	20 (95.2%)	55 (83.3%)	0.28
Ever regular cigarette smoking[a]	4 (19.1%)	16 (24.6%)	0.77
Ever use of a cigar	14 (66.7%)	31 (47.7%)	0.13
Ever use of a pipe	5 (23.8%)	11 (16.9%)	0.52
Ever use of cigarillos	5 (23.8%)	30 (46.2%)	0.07
Ever use of little cigars	2 (9.5%)	7 (10.8%)	1.00
Ever use of smokeless tobacco	5 (23.8%)	17 (26.2%)	0.83
Ever use of snus	0 (0.0%)	6 (9.2%)	0.33
Ever use of hookah	11 (52.4%)	36 (55.4%)	0.81

[a]Ethnicity was self-reported as 'Hispanic or Latino' or 'Not Hispanic or Latino'. Race was self-reported as 'American Indian/Alaskan Native,' 'Asian,' 'Black or African American,' 'Native Hawaiian or Other Pacific Islander,' 'White or Caucasian,' and 'Other,' with multiple choices allowed. The 'Other' category includes non-Hispanic American Indian, Asian, and Pacific Islander. [b]The regular use of a product was defined as using it for at least once a week, for at least a month. [c]Characteristics of e-liquids brought to visit 1. The research staff determined the nicotine form by examining pictures of the participants' usual e-cigarette brands. Brands using cartridges or pods filled with nicotine salts, such as JUUL, Hyde, Elf bar and Breeze Pro, were categorized as nicotine salts, whereas devices designed for user-supplied e-liquid, such as Vaporesso and Caliburn, were categorized as unknown.

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eTable 4. Participant Characteristics and Tobacco Use History

	All Enrolled (n=87) Mean (SD) or No. (%)	**Used study e-liquids[a]** (n=72) Mean (SD) or No. (%)	**Did not use study e-liquids[a]** (n=15) Mean (SD) or No. (%)	p-value
Age	22.4 (1.4)	22.4 (1.4)	22.3 (1.1)	0.78
Female sex assigned at birth	51 (58.6%)	42 (58.3%)	9 (60.0%)	0.91
Race/ethnicity[b]				0.77
Hispanic	6 (6.9%)	6 (8.3%)	0 (0.0%)	
Non-Hispanic Black	4 (4.6%)	3 (4.2%)	1 (6.7%)	
Non-Hispanic White	68 (78.2%)	55 (76.4%)	13 (86.7%)	
Other (e.g., multiple races)	9 (10.3%)	8 (11.1%)	1 (6.7%)	
E-cigarette use characteristics				
Days of use during the past 30 days	27.4 (6.2)	27.4 (6.2)	27.4 (6.1)	0.88
Years of regular e-cigarette use[c]	3.3 (2.1)	3.3 (2.2)	3.2 (1.6)	0.88
Current regular e-cigarette use[c]	84 (97.7%)	71 (98.6%)	13 (92.9%)	0.30
Average Puffs per Day	79.4 (93.4)	85.8 (101.0)	48.9 (26.4)	0.09
Flavor[d]				0.13
Tobacco	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Menthol or Mint	34 (39.5%)	31 (43.1%)	3 (21.4%)	
Other flavor	52 (60.5%)	41 (56.9%)	11 (78.6%)	
Nicotine Form[d]				1.00
Nicotine Salts	66 (75.9%)	54 (75.0%)	12 (80.0%)	
Unknown	21 (24.1%)	18 (25.0%	3 (20.0%)	
Nicotine Concentration, %[c]	4.4 (1.3)	4.5 (1.2)	4.2 (1.5)	0.53
Other tobacco use characteristics				
Ever smoking of a cigarette	75 (86.2%)	64 (88.9%)	11 (73.3%)	0.21
Ever regular cigarette smoking[c]	20 (23.3%)	17 (23.6%)	3 (21.4%)	1.00
Ever use of a cigar	45 (52.3%)	39 (54.2%)	6 (42.9%)	0.56
Ever use of a pipe	16 (18.6%)	15 (20.8%)	1 (7.1%)	0.45
Ever use of cigarillos	35 (40.7%)	30 (41.7%)	5 (35.7%)	0.77
Ever use of little cigars	9 (10.5%)	9 (12.5%)	0 (0.0%)	0.34
Ever use of smokeless tobacco	22 (25.6%)	19 (26.4%)	3 (21.4%)	1.00
Ever use of snus	6 (7.0%)	6 (8.3%)	0 (0%)	0.58
Ever use of hookah	47 (54.7%)	39 (54.2%)	8 (57.1%)	1.00
Number of Visits				0.51
5 Visits	21 (24.1%)	19 (26.4%)	2 (13.3%)	
9 Visits	66 (75.9%)	53 (73.6%)	13 (86.7%)	

[a]72 participants completed the second visit and used at least one study e-liquid, comprising the analytic sample. 15 participants completed only a baseline visit and did not try any study e-liquids. [b]Ethnicity was self-reported as 'Hispanic or Latino' or 'Not Hispanic or Latino'. Race was self-reported as 'American Indian/Alaskan Native,' 'Asian,' 'Black or African American,' 'Native Hawaiian or Other Pacific Islander,' 'White or Caucasian,' and 'Other,' with multiple choices allowed. The 'Other' category includes non-Hispanic American Indian, Asian, and Pacific Islander. [c]The regular use of a product was defined as using it for at least once a week, for at least a month. [d]Characteristics of e-liquids brought to visit 1. The research staff determined the nicotine form by examining pictures of the participants' usual e-cigarette brands. Brands using cartridges or pods filled with nicotine salts, such as JUUL, Hyde, Elf bar and Breeze Pro, were categorized as nicotine salts, whereas devices designed for user-supplied e-liquid, such as Vaporesso and Caliburn, were categorized as unknown.

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eFigure 1. Study device (Evolv Reflex)

The Evolv Reflex was selected for its ability to vape lab-prepared e-liquids and its design similarity to currently available cartridge/pod type e-cigarette devices. The device has been fully characterized and includes puff actuation, 750 mAH battery, 3-25 watt range, 0.5 ohm coil resistance, and 2 mL pod capacity. Emissions testing demonstrated that its nicotine yield under normal use conditions was comparable to typical cigarette yields.

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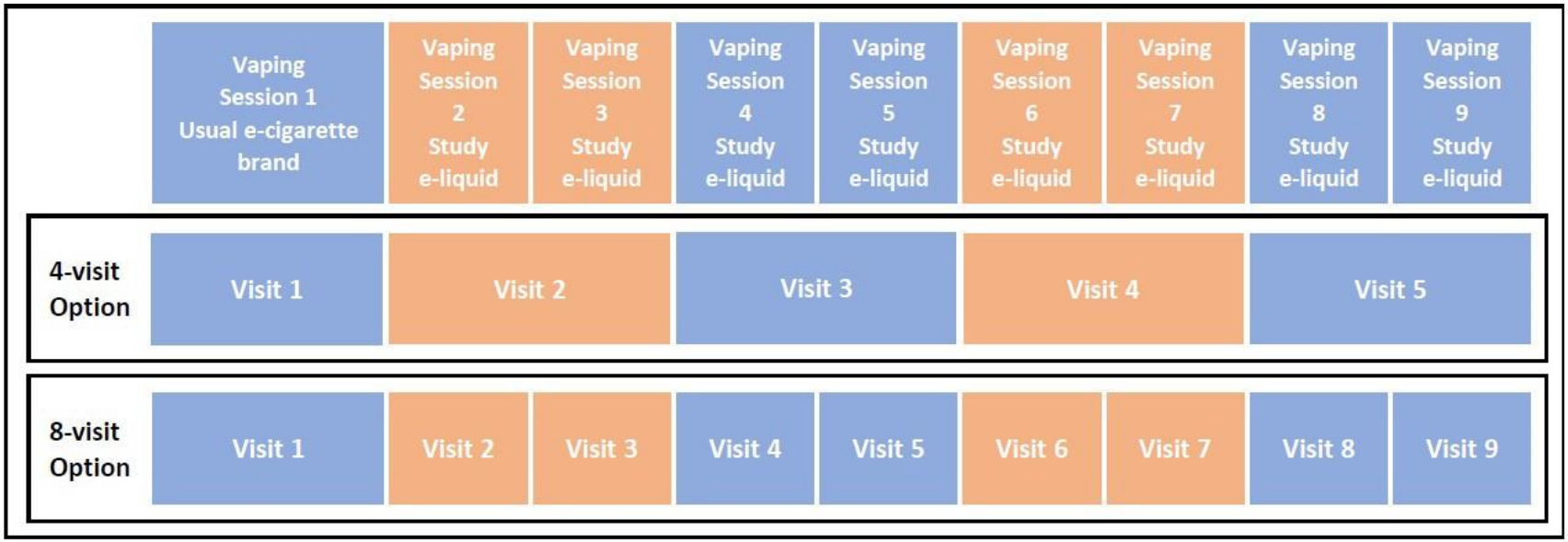
eFigure 2. Study sequence



Note: Participants were required to abstain from nicotine for at least 12 hours before each study visit, with visits separated by a minimum of 48 hours. During the first visit, participants used their usual brand of e-cigarettes. Participants were then given two options for completing the subsequent eight vaping sessions: either in four or eight lab visits based on their preference. For these sessions, the Evolv Reflex e-cigarette device was used, which was set to a constant constant wattage of 8W, and prefilled with one of the eight study e-liquids. The e-liquids varied in nicotine form (freebase vs. salt-based nicotine), nicotine concentration (1% vs. 5% w/w), and flavor (menthol vs. tobacco) and were administered in a randomly assigned order.

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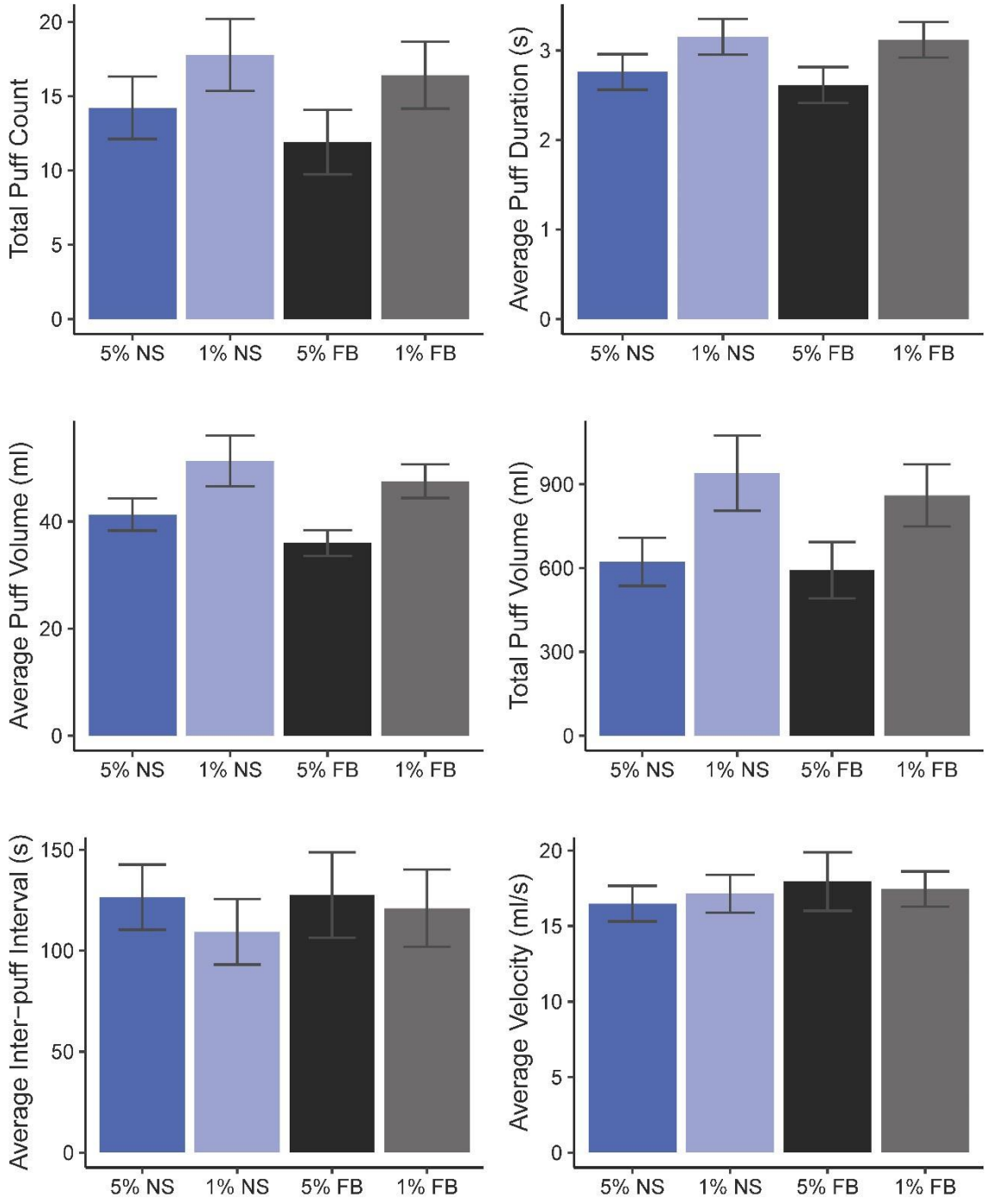
eFigure 3. Topography during the 30-minute ad libitum vaping session by nicotine concentration and form.



VAS: visual analog scale; NS: nicotine salts; FB: freebase nicotine. The boxes represent the means, and the lines represent the 95% confidence intervals. The unit measures were n for total puff count, seconds for average puff duration, and milliliters (ml) for the average puff volume and total puff volume.

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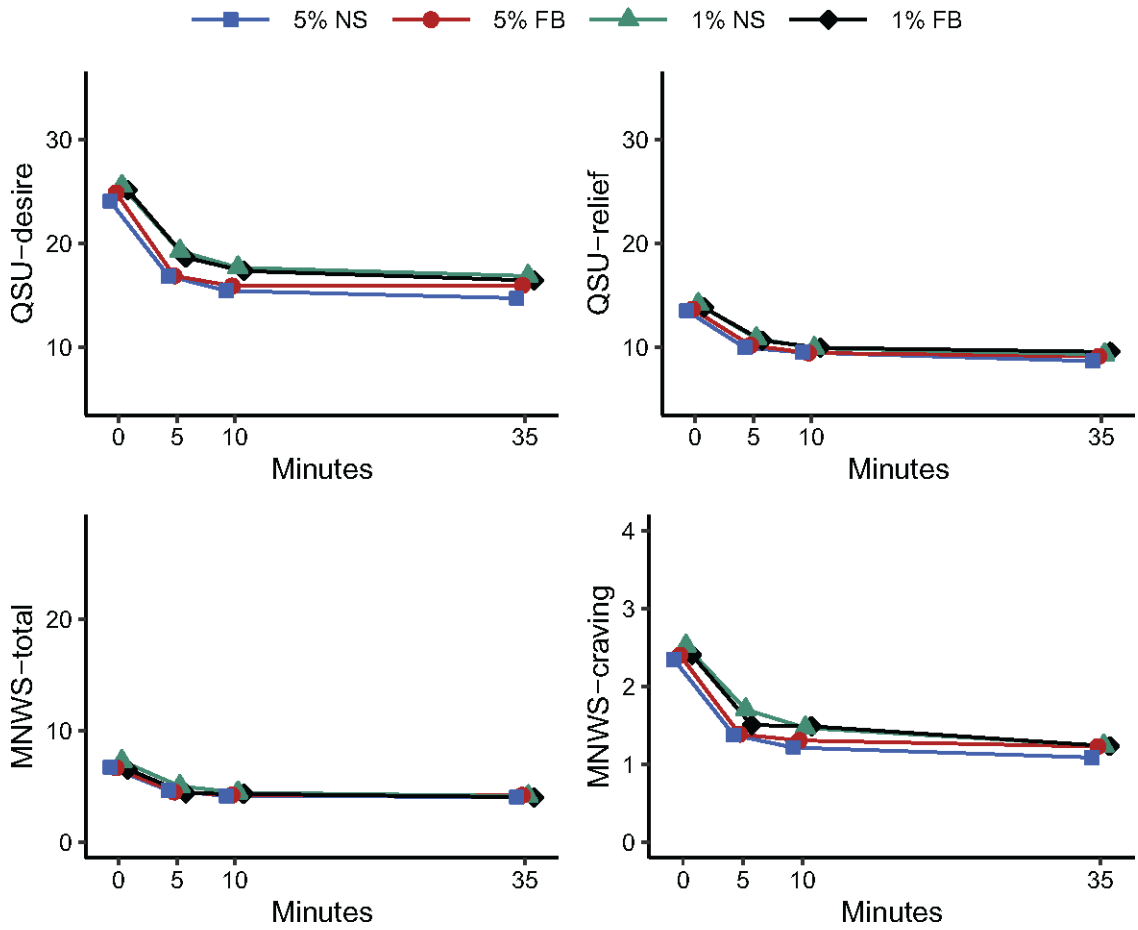
eFigure 4. Urges and cravings for vaping



QSU: Questionnaire of Smoking Urges; MNWS: Minnesota Nicotine Withdrawal Scale. QSU-desire and QSU-relief ranged from 1 to 35. MNWS-total ranged from 0 to 32. MNWS-craving ranged from 0 to 4.

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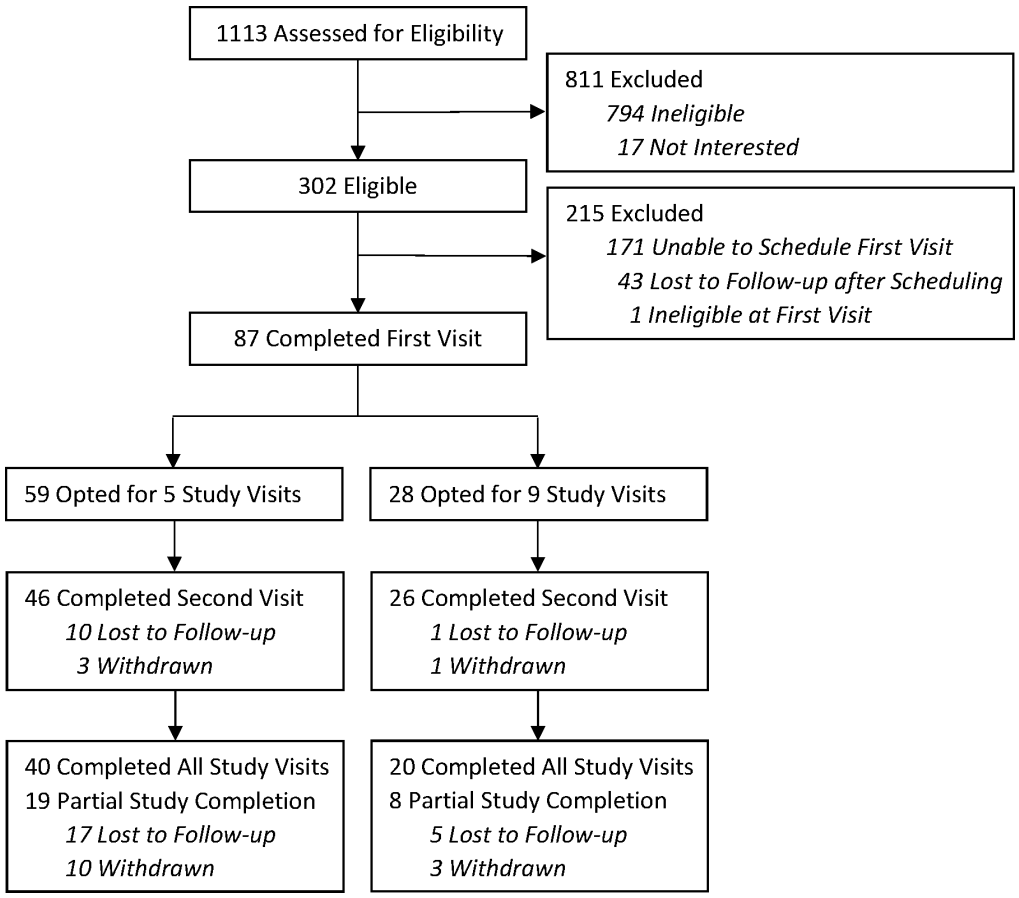
eFigure 5. CONSORT diagram



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eReference

1. Crenshaw MD, Tefft ME, Buehler SS, Brinkman MC, Clark PI, Gordon SM. Determination of nicotine, glycerol, propylene glycol and water in electronic cigarette fluids using quantitative (1) H NMR. *Magn Reson Chem*. Nov 2016;54(11):901-904. doi:10.1002/mrc.4498

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