

Results

Participant characteristics

A total of 560 smokers were recruited and randomized to either combined NRT group (274 participants) or single NRT group (286 participants) for smoking cessation from five clusters (112 each). 21 (3.75%) smokers withdrew from the study, 14 (4.9%) from the single NRT group and 7 (2.6%) from the combined group (Figure 1. Consort workflow diagram). There was no significant difference between the two groups ($p=0.138$). At baseline, most of the participants were male (477, 85.2%) and married (424, 75.7%), the average age was 50.48 years. Regarding the background smoking history, on average, the participants smoked 18.56 cigarettes per day for 32.05 years, i.e., 29.81 pack years. In terms of nicotine dependence, the average Fagerstrom score was 5.71 (moderate), and average baseline CO level was 20.59, for both groups. 56.6% of smokers were heavy smokers in both the single and combined NRT groups. About one third (185, 33.0%) of the participants had cardiovascular (CVS) disease, 20.2% had endocrine disease, and 5.9% had respiratory disease. Overall, no significant differences were detected between single NRT and combined NRT groups for all characteristics in **Table 1**.

Primary outcome

Among observed data, smoking abstinent rate was 21.6% for single NRT group and 30.2% for combined NRT group at 52 weeks ($OR=1.57$, $p=0.058$); similar adjusted odds ratio (1.50, $p=0.073$) was obtained under the imputation scenario of 'missing was non-quitter' (**Table 2**). Over the study period, participants in combined NRT group were significantly more likely to quit smoking than those in single NRT group ($OR=1.41$, $p=0.002$). The treatment effect was also similar ($OR=1.43$, $p<0.001$) after imputing missing records as non-quitter. After adjusting for potential confounders, minor decrease of treatment effect at 52 weeks ($AOR=1.45$, $p=0.138$) and overall treatment effect ($AOR=1.34$, $p=0.013$) was detected for complete data. For imputed data, the result remains unchanged for overall treatment effect ($AOR=1.43$, $p=0.0001$) and slightly decreased at 52 weeks ($AOR=1.49$, $p=0.086$). As shown in **Figure 2(a)**, point smoking abstinent rate was higher for combined NRT group than single NRT group at each assessment visit, especially for assessment at 26 and 52 weeks. For both groups, treatment effect was optimum at 4 weeks and attenuated with time. There was no crossing between the two lines during the follow-up visits, indicating there was no interaction between treatment and time, which was confirmed by the test on the interaction term in the GEE model (coefficient not reported). After imputing missing data for the scenario of 'missing was non-quitter', the point smoking abstinent rate was lower for both groups at each assessment visit, but the differences between two groups and time trend stayed similar with the complete data **Figure 2(b)**.

Secondary outcome

For secondary results, largest treatment effect was found at 26 weeks, participants in combined NRT group were 1.71 times likely to quit smoking than those in single NRT group ($p=0.039$) for complete data. After imputation, there was significant treatment effect at 4 weeks ($OR=1.43$, $p=0.048$). Estimates of treatment effect from logistic regression with and without adjustment for age, sex, baseline CO and cluster were reported in **Table 2**. In this study, 69.6% (1560/560x4) of outcome records were obtained; highest missing rate was at 26 weeks (36.1%) and lowest at 4 weeks (17.9%). There was no significant difference in the missingness between single NRT and combined NRT groups at each visit (**Table 3**). From the missingness pattern plot, no obvious differences could be seen between two treatment groups across all visits **Figure 3**. Sub-analysis showed that baseline age and

number of years smoked were significantly associated with missingness at 52 weeks, participants were younger (average age 48.7 vs. 51.4, p-value=0.014) and had less years smoked (30.3 vs. 32.9, p-value=0.021). Sex, baseline CO level, baseline Fagerstrom score, number of cigarettes smoked per day and compliance (percentage of total patches used) were not significantly associated with missingness at 52 weeks.

Side effect profile

Overall, 3.4% smokers developed side effects after using NRT. The commonest side effect was skin itchiness and rash (**Table 4**). In the single NRT group, 12 (4.2%) reported side effects from nicotine patch. In the combined NRT group, 7 (2.6%) reported side effects from NRT. There was no significant difference between the two groups (p=0.315).

Discussion

This study helps us to understand more on the effect of nicotine replacement therapy on smoking cessation, both monotherapy and combined NRT, in Chinese people. To my knowledge, this is the first interventional study in our locality. Smokers in both groups had high nicotine dependence as shown by their average high Fagerstrom score. On average, the smokers smoked 18 cigarettes a day and for more than 31 years. Combined NRT showed a higher abstinence rate at all follow up intervals: 4, 12, 26 and 52 weeks in both complete data strategy and imputed data strategy. Combined NRT was statistically more superior to single NRT at 26 weeks with complete data strategy (26.4% vs 17.4%). However, with the imputed data strategy, combined NRT was only statistically superior to single NRT at 4 weeks (35.8% vs 28%). The imputed data strategy was adopted because of the high rate in loss of follow up, which was conservative and, thus, decreased the abstinence rates for both groups.

Nevertheless, after applying imputation strategy and GEE model, the statistical power was increased to 93.7% and the study showed significant treatment effect across all visits. The study showed that combined NRT was significantly more superior to single NRT at 4 weeks (OR=1.43, p=0.048) and overall (OR=1.43, p<0.001). The superior effect of combined NRT could be detected as early as 4 weeks after quit date and the effect attenuated with time as confirmed by the GEE model. This result was similar to that noted in the network meta-analysis⁹, which showed combined NRT vs NRT patch OR was 1.43 (95% CI, 1.08 to 1.91) at 6 months or longer after quitting.

In general, the use of NRT required a gradual tapering regimen over 8 to 12 weeks. In our study, it was shown that a total of 8 weeks of NRT was efficient enough to show better abstinence rates in sustaining overall. Besides, the low rate of side effects (2.6%) in the combined group also reassured that it is equally safe as single NRT to use for smoking cessation. In some studies, the common side effects such as skin itchiness and rash could occur in up to 10 to 20%³⁷ of users.

The study is not without limitations. In our study, only 70% of the total records were analysed due to a high rate of loss in follow up, which had exceeded our planned 10%. It had affected the overall statistical power of the study, by decreasing the statistical power to 54.1% and 47.4% at 26 and 52 weeks, respectively. In order to minimize the

effect, GEE was used for repeated measures and control for time*treatment interaction with all available records. This had helped to increase the statistical power increased to over 90%. The high rate in loss in follow up also had affected the abstinence rates. Further sub-analysis was carried out to review the pattern in missing data and the association with either treatment group. There was no significant difference in the missingness in both treatment groups. In fact, the sub-analysis showed that younger smokers and those with less years of smoking were significantly associated with higher missing data in both treatment groups. Based on these observations, the missingness was likely to be the result of a random pattern. Thus, a conservative single imputation strategy 'missing as non-quitter' was employed instead of multiple imputation strategy. With the use of conservative single imputation strategy "missing as non-quitter", the abstinent rates for 26 weeks for combined NRT (26.4% vs 36.5%) and single NRT (21.6% vs 23.4%) were lower than anticipated.

The reasons for this high loss in follow up could be variable. Our study showed that it was associated with younger smokers, which could be due to their busy life and work schedule, or change in residence. Further studies can be focused in younger smokers to enhance their smoking cessation.

Conclusion

Smokers given 8 weeks of combined NRT with nicotine patch and gum had higher abstinence rates at 4, 12, 26 and 52 weeks compared with single NRT and were more likely to quit over the study period. Results also showed that the regimen of combined NRT was as safe as single NRT. Thus, the use of combined NRT should be further promoted in smoking cessation clinics in our community.

Results

Figure 1. Consort workflow diagram

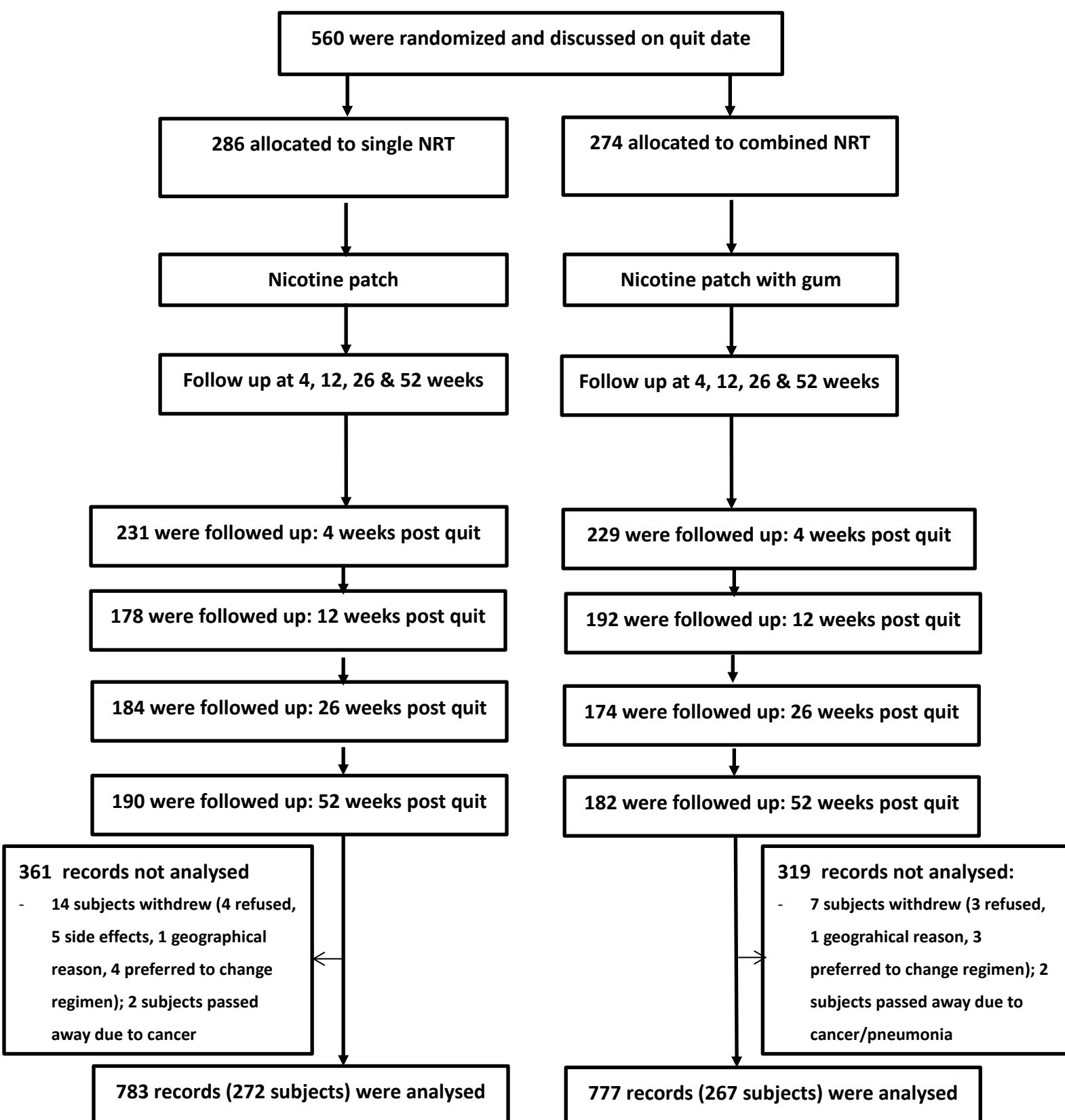


Table 1. Baseline characteristics by treatment groups

Characteristic	Single NRT (N=286)	Combined NRT (N=274)	p-value
Age (in years), mean (SD)	50.56 (12.08)	50.41 (12.30)	0.884
Male, No. (%)	236 (82.5)	241 (88.0)	0.091
Marital Status, No. (%)			0.386
Single	48 (16.8)	37 (13.5)	
Married	208 (72.7)	216 (78.8)	
Divorced/Separated	23 (8.0)	17 (6.2)	
Widowed	7 (2.4)	4 (1.5)	
Education, No. (%)			0.565
No formal schooling	3 (1.0)	7 (2.6)	
Primary	60 (21.0)	61 (22.3)	
Secondary	203 (71.0)	187 (68.2)	
Tertiary	20 (7.0)	19 (6.9)	
Work status, No. (%)			0.310
Unemployed	61 (21.3)	47 (17.2)	
Full time	181 (63.3)	188 (68.6)	
Part time	16 (5.6)	8 (2.9)	
Retired	20 (7.0)	24 (8.8)	
Housewife	8 (2.8)	7 (2.6)	
Payment status, No. (%)			0.506
Entitled patients	234 (81.8)	220 (80.3)	
Waivers	18 (6.3)	24 (8.8)	
Hospital Authority staff/Civil servants	29 (10.1)	28 (10.2)	
Others	5 (1.7)	2 (0.7)	
Cluster, No. (%)			0.946
HKEC	56 (19.6)	56 (20.4)	
KCC	55 (19.2)	57 (20.8)	
KEC	61 (21.3)	51 (18.6)	
NTEC	57 (19.9)	55 (20.1)	
NTWC	57 (19.9)	55 (20.1)	
Co-existing diseases			
Respiratory disease, No. (%)	18 (6.3)	15 (5.5)	0.816
CVS disease, No. (%)	105 (36.7)	80 (29.2)	0.072
Endocrine disease, No. (%)	59 (20.6)	54 (19.7)	0.868
Smoking history			
No. of cigarettes/day used, mean (SD)	18.44 (6.90)	18.68 (6.88)	0.683
Heavy Smoker (≥ 20 cigarettes/day), No. (%)	162 (56.6)	155 (56.6)	0.988
Years smoked, mean (SD)	31.93 (11.94)	32.17 (12.43)	0.817

Results_completed on 23 Nov 2018			
Pack-years, mean (SD)	29.45 (15.37)	30.18 (16.65)	0.591
Fagerstrom score, mean (SD)	5.57 (2.01)	5.85 (1.79)	0.090
Fagerstrom score, No. (%)			0.347
Low dependence (0-2)	22 (7.7)	12 (4.4)	
Low to Moderate (3-4)	58 (20.3)	51 (18.6)	
Moderate (5-7)	160 (55.9)	161 (58.8)	
High dependence (8+)	46 (16.1)	50 (18.2)	
Baseline CO level (ppm), mean (SD)	20.36 (12.03)	20.83 (12.49)	0.652

Note:

NRT: nicotine replacement therapy.

SD: standard deviation.

For all continuous variables, mean and SD were reported and p-values were calculated from two sample t-test; for all categorical variables, number and proportion were reported and p-values were calculated from Chi-square test.

Table 2. Test for Treatment Effect on Primary Outcome - Smoking Quit Status.

Outcome	Single NRT			Combined NRT			OR	p-value	AOR	p-value
	No. of	Abstinent	Available	No. of	Abstinent	Available				
	Success	Rate (%)	No.	Success	Rate (%)	No.				
Complete Data										
4 weeks	80	34.6	231	98	42.8	229	1.41	0.073	1.35	0.136
12 weeks	48	27.0	178	60	31.2	192	1.23	0.370	1.13	0.604
26 weeks	32	17.4	184	46	26.4	174	1.71	0.039*	1.53	0.110
52 weeks	41	21.6	190	55	30.2	182	1.57	0.058	1.45	0.138
GEE	201	25.7	783	259	33.3	777	1.41	0.002**	1.34	0.013**
Imputed Data										
4 weeks	80	28.0	286	98	35.8	274	1.43	0.048*	1.38	0.087
12 weeks	48	16.8	286	60	21.9	274	1.39	0.130	1.37	0.153
26 weeks	32	11.2	286	46	16.8	274	1.60	0.057	1.56	0.080
52 weeks	41	14.3	286	55	20.1	274	1.50	0.073	1.49	0.086
GEE	201	17.6	1114	259	23.6	1096	1.43	<0.001**	1.43	0.001**

Notes:

NRT: nicotine replacement therapy.

Complete Data: available records without any imputation.

Imputed Data: missing records were imputed as 'failure' (non-quitter) for the primary outcome.

OR: odds ratio. At each visit, crude odds ratio (combined NRT vs. single NRT) and p-value was reported from logistic regression without adjustment; for repeated measures, adjusted odds ratio and p-value was reported from Generalized Estimating Equation (GEE) adjusted for time.

AOR: adjusted odds ratio. At each visit, adjusted odds ratio (combined NRT vs. single NRT) and p-value was reported from logistic regression with adjustment for age, sex, baseline CO and cluster; for

repeated measures, adjusted odds ratio and p-value was reported from GEE adjusted for time, age, sex, baseline CO and cluster.

Table 3. Obtained Primary Outcome across Visits, by Treatment Group.

	Single NRT	Combined NRT	p-value ^a
Expected N	286	274	-
4 weeks	231 (80.8%)	229 (83.6%)	0.449
12 weeks	178 (62.2%)	192 (70.1%)	0.062
26 weeks	184 (64.3%)	174 (63.5%)	0.907
52 weeks	190 (66.4%)	182 (66.4%)	1.000
All visits	783 (69.3%)	777 (70.9%)	0.219 ^b

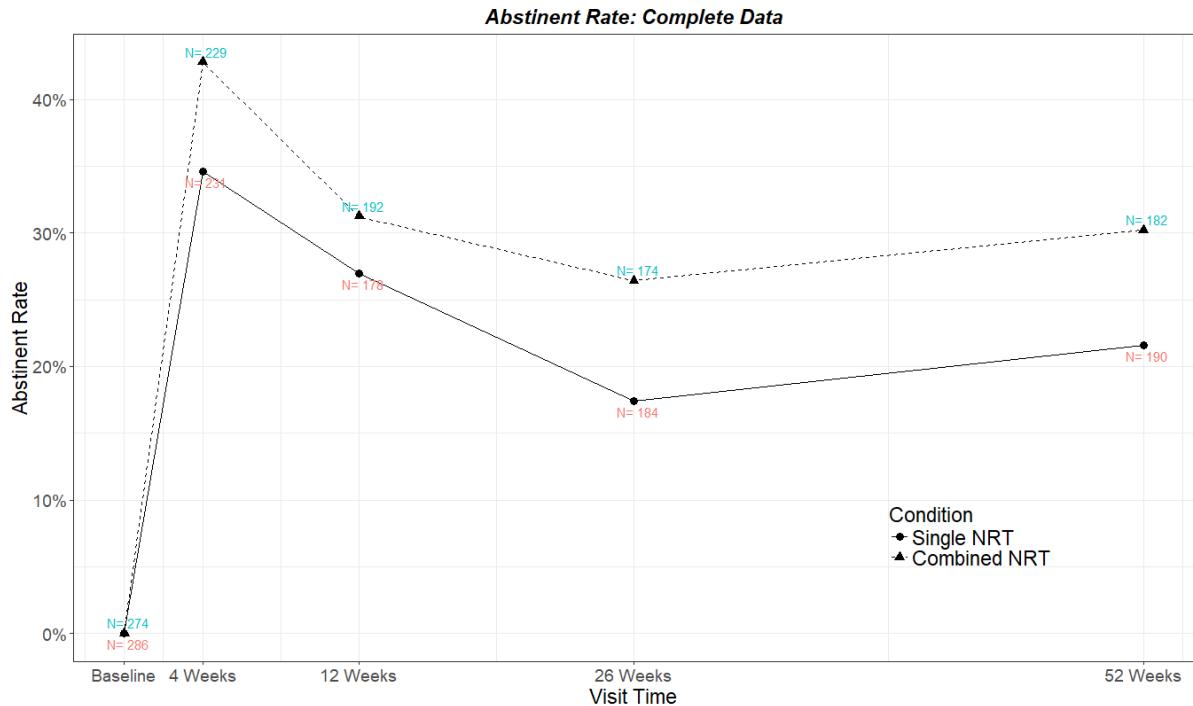
Notes:

a. P-values from Chi-square test.

b. P-value from Mantel-Haenszel Chi-squared test with continuity correction.

Table 4. Reported side effects in both treatment groups

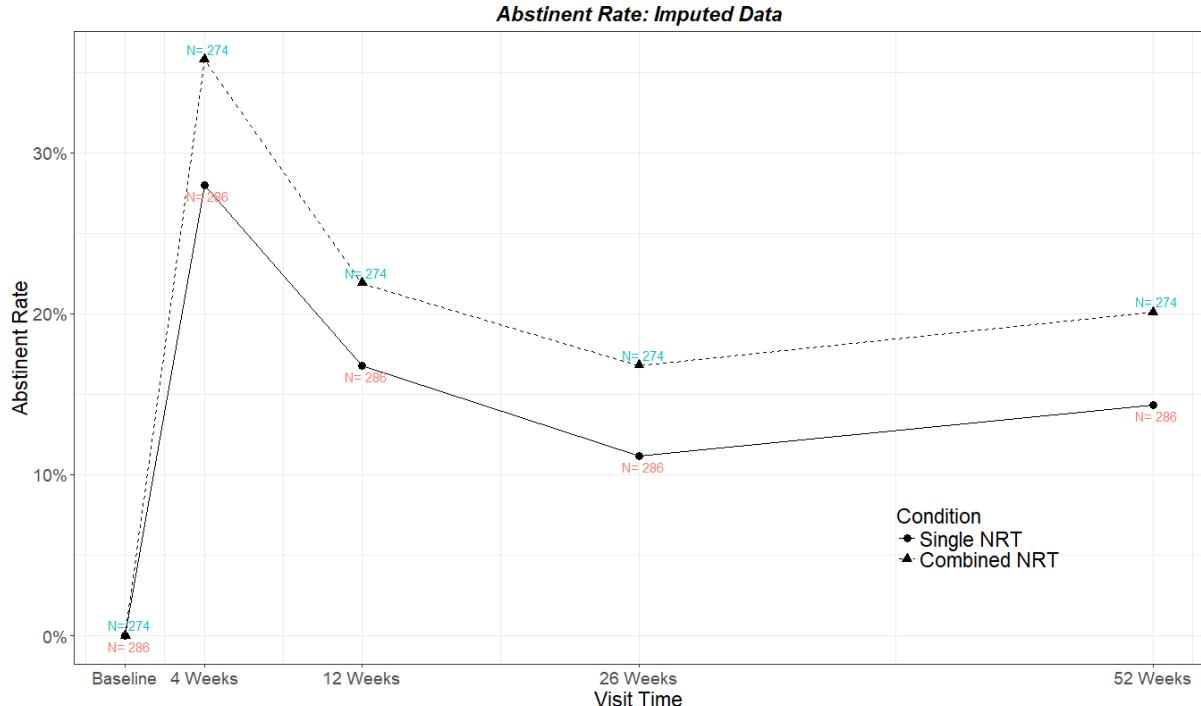
	Single NRT (N=286)	Combined NRT (N=274)	p-value
No of patients reported side effects	12 (4.2)	7 (2.6)	0.315
Frequency of side effects			
Abdominal pain	1	0	
Dizziness	1	0	
Dreams	1	0	
Insomnia	1	0	
Palpitation	3	0	
Skin itchiness	3	3	
Skin rash	6	4	
Stomach	1	1	

Figure 2(a). Abstinent Rate across Visits, by Treatment Group: Complete Data.

Notes:

NRT: nicotine replacement therapy.

Abstinent rate, i.e., proportion of successful quitters was calculated at 4 weeks, 12 weeks, 26 weeks and 52 weeks for complete data (all available records).

Figure 2(b). Abstinent Rate across Visits, by Treatment Group: Imputed Data

Note:

NRT: nicotine replacement therapy.

Abstinent rate, i.e., proportion of successful quitters was calculated at 4 weeks, 12 weeks, 26 weeks and 52 weeks for worst scenario: missing records were imputed as 'failure' (non-quitter).

Figure 3. Missing pattern analysis for primary outcome.

Missing pattern analysis for primary outcome.

There's no significant difference in missingness by treatment group at each visit (see table below).

	Single NRT	Combined NRT	p-value
	(Expected N =286)	(Expected N =274)	
	N missing (%)		
4 weeks	55 (19.2)	45 (16.4)	0.449
12 weeks	108 (37.8)	82 (29.9)	0.062
26 weeks	102 (35.7)	100 (36.5)	0.907
52 weeks	96 (33.6)	92 (33.6)	1

(light area means missing)

